

(12) **UK Patent Application** (19) **GB** (11) **2 373 186** (13) **A**

(43) Date of A Publication 18.09.2002

(21) Application No 0104534.3

(22) Date of Filing 23.02.2001

(71) Applicant(s)
AstraZeneca AB
(Incorporated in Sweden)
151 85 Södertälje, Sweden

(72) Inventor(s)
Ash Bahl
Matthew Perry
Brian Springthorpe

(74) Agent and/or Address for Service
Francis John Tierney
Astrazeneca, Global Intellectual Property, Mereside,
MACCLESFIELD, Cheshire, SK10 4TG,
United Kingdom

(51) INT CL⁷

A61K 31/4468 31/4525 31/453 31/4535 31/454 31/4545
31/46 31/496 31/497 31/498 31/506 31/517 31/519
31/52 45/00 // A61P 11/06 37/08

(52) UK CL (Edition T)

A5B BJA B180 B327 B42Y B420 B421 B422 B426 B43Y
B431 B44Y B440 B441 B442 B444 B446 B45Y B451
B48X B48Y B480 B481 B482 B483 B484 B485 B49Y
B490 B491 B492 B493 B50Y B510 B511 B512 B513
B52Y B521 B54Y B540 B541 B542 B543 B544 B546
B55Y B550 B551 B552 B553 B554 B556 B56Y B565
B566 B57Y B575 B576 B58Y B586 B59Y B595 B596
B60Y B605 B606 B61Y B616 B64Y B640 B642 B644
B645 B65X B65Y B650 B656 B66Y B660 B661 B666
B67X B67Y B670 B671 B673 B675 B676
U1S S1321 S2416

(56) Documents Cited

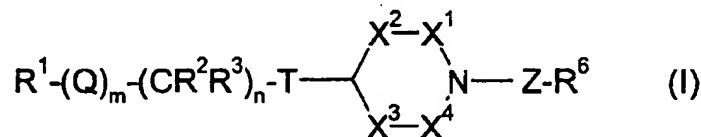
WO 2002/032893 A2 WO 2001/060407 A2
WO 1998/006394 A1 US 6103735 A
CAPLUS Abstract Accession No. 2001:79915 &
BioDrugs Vol. 14, No. 6, 2000, pages 371-387

(58) continued overleaf

(54) Abstract Title

Pharmaceutical combinations of a CCR3 antagonist and a compound which is useful treatment of asthma, allergic disease or inflammation

(57) The invention provides a pharmaceutical combination comprising a compound of formula (I):



wherein R^1 , R^2 , R^3 , R^6 , Z , Q , m , n , X^1 , X^2 , X^3 , X^4 and T are as defined in the specification, and a histamine antagonist, a steroid, a leukotriene modulator, a human cytokine, a beta-agonist, a phosphodiesterase inhibitor or an antibody; a process for preparing such a combination and the use of such a combination in therapy (especially the treatment of asthma or rhinitis). In particular, the compounds of formula (I) are substituted piperidines and substituted 8-azabicyclo[3.2.1]octanes and are described as being CCR3 antagonists.

GB 2 373 186 A

(58) Field of Search

UK CL (Edition T) A5B

INT CL⁷ A61K 31/4468 31/4523 31/4525 31/453

31/4535 31/454 31/4545 31/46 31/496 31/497 31/498

31/506 31/517 31/519 31/52

Online: PAJ, EPODOC, WPI, CAS-ONLINE

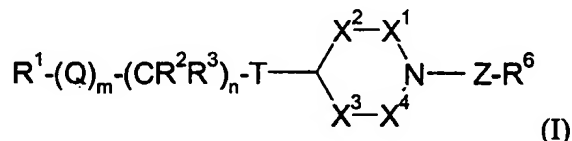
PHARMACEUTICAL COMBINATION

The present invention relates to a pharmaceutical combination comprising a piperidine CCR3 antagonist compound and compound useful in the treatment of asthma, allergic disease or inflammation, to a process for preparing such a combination and to the use of such a combination in therapy.

Chemokines play an important role in immune and inflammatory responses in various diseases and disorders, including asthma and allergic diseases, as well as autoimmune pathologies such as rheumatoid arthritis and atherosclerosis.

CCR3 antagonists are disclosed in WO00/58305.

The present invention provides a pharmaceutical combination comprising a compound of formula (I):



wherein

Z is CR^4R^5 , $C(O)$ or $CR^4R^5-Z^1$;

Z^1 is C_{1-4} alkylene (such as CH_2), C_{2-4} alkenylene (such as $CH=CH$) or $C(O)NH$;

R^1 represents a C_{1-12} alkyl group optionally substituted by one or more substituents independently selected from cyano, hydroxyl, C_{1-6} alkoxy (such as methoxy or ethoxy), C_{1-6} alkylthio (such as methylthio), C_{3-7} cycloalkyl (such as cyclopropyl), C_{1-6} alkoxycarbonyl (such as methoxycarbonyl) and phenyl (itself optionally substituted by one or more of halogen, nitro, cyano, C_{1-6} alkyl, C_{1-6} haloalkyl (such as CF_3), phenyl(C_{1-6} alkyl) (such as benzyl), C_{1-6} alkoxy, C_{1-6} haloalkoxy, $S(O)_2(C_{1-6}$ alkyl), $C(O)NH_2$, carboxy or C_{1-6} alkoxycarbonyl); or

R^1 represents C_{2-6} alkenyl optionally substituted by phenyl (itself optionally substituted by one or more of halogen, nitro, cyano, C_{1-6} alkyl, C_{1-6} haloalkyl, phenyl(C_{1-6} alkyl), C_{1-6} alkoxy, C_{1-6} haloalkoxy, $S(O)_2(C_{1-6}$ alkyl), $C(O)NH_2$, carboxy or C_{1-6} alkoxycarbonyl); or R^1 represents a 3- to 14-membered saturated or unsaturated ring system which optionally comprises up to two ring carbon atoms that form carbonyl groups and which optionally further comprises up to 4 ring heteroatoms independently selected from nitrogen, oxygen and sulphur, wherein the ring system is optionally substituted by one or more substituents

- independently selected from: halogen, cyano, nitro, oxo, hydroxyl, C₁₋₈ alkyl, C₁₋₆ hydroxyalkyl, C₁₋₆ haloalkyl, C₁₋₆ alkoxy(C₁₋₆ alkyl), C₃₋₇ cycloalkyl(C₁₋₆ alkyl), C₁₋₆ alkylthio(C₁₋₆ alkyl), C₁₋₆ alkylcarbonyloxy(C₁₋₆ alkyl), C₁₋₆ alkylS(O)₂(C₁₋₆ alkyl), aryl(C₁₋₆ alkyl), heterocyclyl(C₁₋₆ alkyl), arylS(O)₂(C₁₋₆ alkyl), heterocyclylS(O)₂(C₁₋₆ alkyl), aryl(C₁₋₆ alkyl)S(O)₂, heterocyclyl(C₁₋₆ alkyl)S(O)₂, C₂₋₆ alkenyl, C₁₋₆ alkoxy, carboxy-substituted C₁₋₆ alkoxy, C₁₋₆ haloalkoxy, C₁₋₆ hydroxyalkoxy, C₁₋₆ alkylcarboxy-substituted C₁₋₆ alkoxy, aryloxy, heterocycloxy, C₁₋₆ alkylthio, C₃₋₇ cycloalkyl(C₁₋₆ alkylthio), C₃₋₆ alkynylthio, C₁₋₆ alkylcarbonylamino, C₁₋₆ haloalkylcarbonylamino, SO₃H, NR⁷R⁸, C(O)NR²³R²⁴, S(O)₂NR¹⁸R¹⁹, S(O)₂R²⁰, R²⁵C(O), carboxyl, C₁₋₆ alkoxycarbonyl, aryl and heterocyclyl; wherein the foregoing aryl and heterocyclyl moieties are optionally substituted by one or more of halogen, oxo, hydroxy, nitro, cyano, C₁₋₆ alkyl, C₁₋₆ haloalkyl, phenyl(C₁₋₆ alkyl), C₁₋₆ alkoxy, C₁₋₆ haloalkoxy, S(O)₂(C₁₋₆ alkyl), C(O)NH₂, carboxy or C₁₋₆ alkoxycarbonyl;
- m is 0 or 1;
- Q represents an oxygen or sulphur atom or a group NR⁹, C(O), C(O)NR⁹, NR⁹C(O) or CH=CH;
- n is 0, 1, 2, 3, 4, 5 or 6 provided that when n is 0, then m is 0;
- each R² and R³ independently represents a hydrogen atom or a C₁₋₄ alkyl group, or (CR²R³)_n represents C₃₋₇ cycloalkyl optionally substituted by C₁₋₄ alkyl;
- T represents a group NR¹⁰, C(O)NR¹⁰, NR¹¹C(O)NR¹⁰ or C(O)NR¹⁰NR¹¹;
- X¹, X², X³ and X⁴ are, independently, CH₂, CHR¹² {wherein each R¹² is, independently, C₁₋₄ alkyl or C₃₋₇ cycloalkyl(C₁₋₄ alkyl)} or C=O; or, when they are CHR¹², the R¹² groups of X¹ and X³ or X⁴, or, X² and X³ or X⁴ join to form a two or three atom chain which is CH₂CH₂, CH₂CH₂CH₂, CH₂OCH₂ or CH₂SCH₂; provided always that at least two of X¹, X², X³ and X⁴ are CH₂;
- R⁴ and R⁵ each independently represent a hydrogen atom or a C₁-C₄ alkyl group;
- R⁶ is aryl or heterocyclyl, both optionally substituted by one or more of: halogen, cyano, nitro, oxo, hydroxyl, C₁₋₈ alkyl, C₁₋₆ hydroxyalkyl, C₁₋₆ haloalkyl, C₁₋₆ alkoxy(C₁₋₆ alkyl), C₃₋₇ cycloalkyl(C₁₋₆ alkyl), C₁₋₆ alkylthio(C₁₋₆ alkyl), C₁₋₆ alkylcarbonyloxy(C₁₋₆ alkyl), C₁₋₆ alkylS(O)₂(C₁₋₆ alkyl), aryl(C₁₋₆ alkyl), heterocyclyl(C₁₋₆ alkyl), arylS(O)₂(C₁₋₆ alkyl), heterocyclylS(O)₂(C₁₋₆ alkyl), aryl(C₁₋₆ alkyl)S(O)₂, heterocyclyl(C₁₋₆ alkyl)S(O)₂, C₂₋₆ alkenyl, C₁₋₆ alkoxy, carboxy-substituted C₁₋₆ alkoxy, C₁₋₆ haloalkoxy, C₁₋₆ hydroxyalkoxy,

C_{1-6} alkylcarboxy-substituted C_{1-6} alkoxy, aryloxy, heterocycloxy, C_{1-6} alkylthio, C_{3-7} cycloalkyl(C_{1-6} alkylthio), C_{3-6} alkynylthio, C_{1-6} alkylcarbonylamino, C_{1-6} haloalkylcarbonylamino, SO_3H , $-NR^{16}R^{17}$, $-C(O)NR^{21}R^{22}$, $S(O)_2NR^{13}R^{14}$, $S(O)_2R^{15}$, $R^{26}C(O)$, carboxyl, C_{1-6} alkoxycarbonyl, aryl and heterocyclyl; wherein the foregoing aryl and heterocyclyl moieties are optionally substituted by one or more of halogen, nitro, cyano, C_{1-6} alkyl, C_{1-6} haloalkyl, phenyl(C_{1-6} alkyl), C_{1-6} alkoxy, C_{1-6} haloalkoxy, $S(O)_2(C_{1-6}$ alkyl), $C(O)NH_2$, carboxy or C_{1-6} alkoxycarbonyl; R^7 , R^8 , R^9 , R^{10} , R^{11} , R^{13} , R^{14} , R^{16} , R^{17} , R^{18} , R^{19} , R^{21} , R^{22} , R^{23} and R^{24} are, independently hydrogen, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} hydroxyalkyl, C_{3-7} cycloalkyl, C_{3-7} cycloalkyl(C_{1-4} alkyl) or phenyl(C_{1-6} alkyl); and, R^{15} and R^{20} are, independently, C_{1-6} alkyl, C_{1-6} hydroxyalkyl, C_{3-6} cycloalkyl, C_{3-7} cycloalkyl(C_{1-4} alkyl) or C_{1-6} alkyl optionally substituted by phenyl; R^{25} and R^{26} are, independently, C_{1-6} alkyl or phenyl (optionally substituted by one or more of halogen, nitro, cyano, C_{1-6} alkyl, C_{1-6} haloalkyl, phenyl(C_{1-6} alkyl), C_{1-6} alkoxy, C_{1-6} haloalkoxy, $S(O)_2(C_{1-6}$ alkyl), $C(O)NH_2$, carboxy or C_{1-6} alkoxycarbonyl); or a pharmaceutically acceptable salt thereof, or solvate thereof, or a solvate of a salt thereof; provided that when T is $C(O)NR^{10}$ and R^1 is optionally substituted phenyl then n is not 0; and a histamine antagonist, a steroid, a leukotriene modulator, a human cytokine, a beta-agonist, a phosphodiesterase inhibitor or an antibody.

Histamine antagonists are, for example, loratidine, desloratidine, fexofenadine, cetirizine, ebastine, astemizole, norastemizole, epinastine or efletirizine.

Steroids are, for example, budesonide, fluticasone, mometasone or rofleponide (such as rofleponide palmitate).

Leukotriene modulators are, for example, montelukast (such as in its sodium salt form), pranlukast, zafirlukast, Z4407 or zafirlukast.

Human cytokines are, for example, recombinant human IL-10 or IL-12.

Beta-agonists are, for example, formoterol, salmeterol or salbutamol.

Phosphodiesterase inhibitors are, for example, SB-207499 (ARIFLO[®]) or theophylline.

Antibodies are, for example, anti-IL-5 antibodies or anti-TNF-antibodies (such as infliximab).

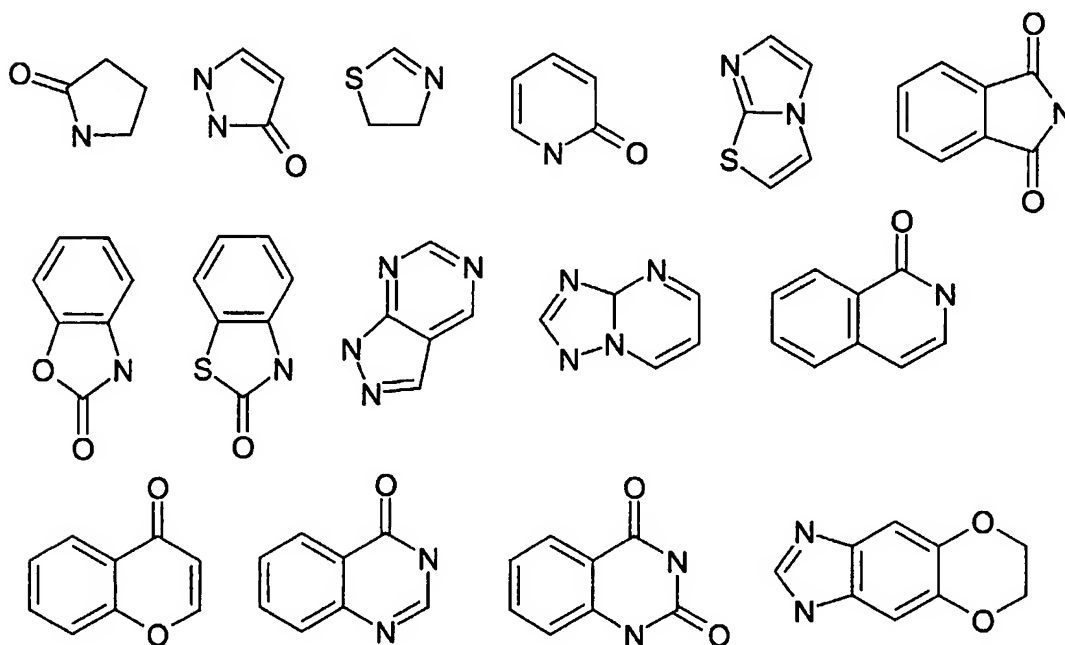
Certain compounds of formula (I) are capable of existing in isomeric forms (for example as tautomers, enantiomers, geometric isomers or diastereomers). The present invention encompasses all such isomers and mixtures thereof in all proportions.

Hydroxyalkyl is, for example, 2-hydroxyethyl-1-yl. Haloalkyl is, for example, CF_3 .
 5 Alkoxy is, for example, methoxy or ethoxy. Alkoxy(C_{1-6} alkyl) is, for example, methoxymethyl or ethoxyethyl. Cycloalkyl is, for example, cyclopropyl or cyclohexyl. Cycloalkyl(C_{1-6} alkyl) is, for example, cyclopropylmethyl. Alkylthio is, for example, methylthio or ethylthio. Alkylthio(C_{1-6} alkyl) is, for example, methylthiomethyl. Alkylcarbonyloxy(C_{1-6} alkyl) is, for example, $\text{CH}_3\text{C}(\text{O})\text{OCH}_2$. $\text{S}(\text{O})_2(\text{C}_{1-6}$ alkyl) is, for example, $\text{CH}_3\text{S}(\text{O})_2$. Alkyl $\text{S}(\text{O})_2(\text{C}_{1-6}$ alkyl) is, for example, $\text{CH}_3\text{S}(\text{O})_2\text{CH}_2$. Aryl(C_{1-6} alkyl) is, for example, benzyl, 2-phenyleth-1-yl or 1-phenyleth-1-yl. Heterocyclyl(C_{1-6} alkyl) is, for example, heterocyclylmethyl. Aryl $\text{S}(\text{O})_2(\text{C}_{1-6}$ alkyl) is, for example, phenyl $\text{S}(\text{O})_2\text{CH}_2$. Heterocyclyl $\text{S}(\text{O})_2(\text{C}_{1-6}$ alkyl) is, for example, heterocyclyl $\text{S}(\text{O})_2\text{CH}_2$. Aryl(C_{1-6} alkyl) $\text{S}(\text{O})_2$ is, for example, benzyl $\text{S}(\text{O})_2$. Heterocyclyl(C_{1-6} alkyl) $\text{S}(\text{O})_2$ is, for example, heterocyclyl $\text{CH}_2\text{S}(\text{O})_2$. Alkenyl is, for example, vinyl or allyl. Carboxy-substituted C_{1-6} alkoxy is, for example, $\text{HOC}(\text{O})\text{CH}_2\text{CH}_2\text{O}$. Haloalkoxy is, for example, OCF_3 . Hydroxyalkoxy is, for example, $\text{HOCH}_2\text{CH}_2\text{O}$. Alkylcarboxy-substituted C_{1-6} alkoxy is, for example, $\text{CH}_3\text{OC}(\text{O})\text{CH}_2\text{CH}_2\text{O}$. Aryloxy is, for example, phenoxy. Heterocycloxy is, for example, pyridinyloxy or pyrimidinyloxy. C_{3-7} cycloalkyl(C_{3-6} alkylthio) is, for example, cyclopropyl CH_2S . Alkynylthio is, for example, propargylthio. Alkylcarbonylamino is, for example, acylamino. Haloalkylcarbonylamino is, for example, $\text{ClCH}_2\text{C}(\text{O})\text{NH}$. Alkoxy-carbonyl is, for example, $\text{CH}_3\text{OC}(\text{O})$.

Aryl is a carbocyclic aromatic ring optionally fused to one or more carbocyclic rings. Aryl is, for example, phenyl, naphthyl or indanyl.

25 Heterocyclyl is an aromatic or non-aromatic ring system preferably comprising up to 6 (preferably up to 4) heteroatoms selected from the group comprising nitrogen, oxygen and sulphur, and preferably comprising one, two or three 5- or 6-membered rings. Heterocyclyl is, for example, furyl, thienyl, pyrrolyl, 2,5-dihydropyrrolyl, thiazolyl, pyrazolyl, oxazolyl, isoxazolyl, imidazolyl, 1,2,4-oxadiazolyl, 1,3,4-oxadiazolyl, 1,2,3-triazolyl, 1,2,4-triazolyl, tetrazolyl, pyrrolidinyl, piperidinyl, piperazinyl, morpholinyl,
 30 pyridinyl (for example 2-pyridinyl, 3-pyridinyl or 4-pyridinyl), pyrimidinyl (for example 2-pyrimidinyl or 4-pyrimidinyl), pyrazinyl, pyridazinyl, indolyl, 2,3-dihydroindolyl,

benzo[b]furyl, benz[b]thienyl, 2,3-dihydrobenz[b]thienyl (for example 1-dioxo-2,3-dihydrobenz[b]thienyl), benzimidazolyl, benztriazolyl, benzoxazolyl, benzthiazolyl, 2,3-dihydrobenzthiazolyl (for example 2,3-dihydrobenzthiazol-2-onyl which is also known as 2-oxo-1,3-benzothiazol-3(2H)-yl), 1,2,3-benzothiadiazolyl, 1,2,3-benzoxadiazolyl, 2,1,3-benzothiadiazolyl, 2,1,3-benzoxadiazolyl, quinoxalyl, dihydro-1-benzopyryliumyl (for example a coumarinyl or a chromenonyl), 1,3-benzodioxolyl (also known as 1,2-methylenedioxyphenyl), 3,4-dihydro-1H-2,1-benzothiazinyl (for example 2-dioxo-3,4-dihydro-1H-2,1-benzothiazinyl), purine (for example 1H-purine or 9H-purine), 1H-pyrazolo[3,4-d]pyrimidinyl, thieno[2,3-d]pyrimidinyl, thieno[3,2-d]pyrimidinyl, quinolinyl (for example 2-quinolinyl, 3-quinolinyl or 4-quinolinyl), isoquinolinyl, quinazolinyl or dibenzothiophenyl; or a ring as shown below:

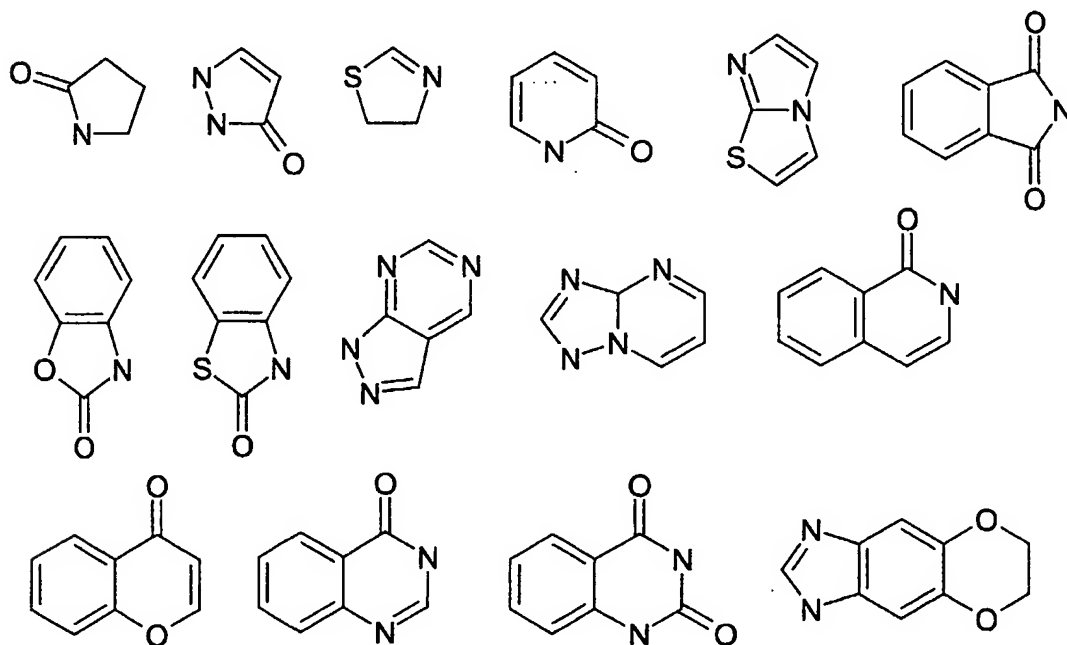


The group R^1 may represent an optionally substituted 3- to 14-membered (especially 5- to 10-membered) saturated or unsaturated ring system which optionally comprises one or two ring carbon atoms that form carbonyl groups and which optionally further comprises one, two, three or four ring heteroatoms independently selected from nitrogen, oxygen and sulphur. Examples of R^1 ring systems, which can be monocyclic or polycyclic, include cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, phenyl, naphthyl, indanyl, furyl, thienyl, pyrrolyl, 2,5-dihydropyrrolyl, thiazolyl, pyrazolyl, oxazolyl, isoxazolyl, imidazolyl, 1,2,4-oxadiazolyl, 1,3,4-oxadiazolyl, 1,2,3-triazolyl, 1,2,4-triazolyl,

tetrazolyl, pyrrolidinyl, piperidinyl, piperazinyl, morpholinyl, pyridinyl (for example 2-pyridinyl, 3-pyridinyl or 4-pyridinyl), pyrimidinyl (for example 2-pyrimidinyl or 4-pyrimidinyl), pyrazinyl, pyridazinyl, indolyl, 2,3-dihydroindolyl, benzo[b]furyl, benz[b]thienyl, 2,3-dihydrobenz[b]thienyl (for example 1-dioxo-2,3-

5 dihydrobenz[b]thienyl), benzimidazolyl, benztriazolyl, benzoxazolyl, benzthiazolyl, 2,3-dihydrobenzthiazolyl (for example 2,3-dihydrobenzthiazol-2-onyl which is also known as 2-oxo-1,3-benzothiazol-3(2H)-yl), 1,2,3-benzothiadiazolyl, 1,2,3-benzoxadiazolyl, 2,1,3-benzothiadiazolyl, 2,1,3-benzoxadiazolyl, quinoxalinyl, dihydro-1-benzopyryliumyl (for example a coumarinyl or a chromenonyl), 1,3-benzodioxolyl (also known as 1,2-

10 methylenedioxyphenyl), 3,4-dihydro-1H-2,1-benzothiazinyl (for example 2-dioxo-3,4-dihydro-1H-2,1-benzothiazinyl), purine (for example 1H-purine or 9H-purine), 1H-pyrazolo[3,4-d]pyrimidinyl, thieno[2,3-d]pyrimidinyl, thieno[3,2-d]pyrimidinyl, quinolinyl (for example 2-quinolinyl, 3-quinolinyl or 4-quinolinyl), isoquinolinyl, quinazolinyl or dibenzothiophenyl; or a ring as shown below:



15

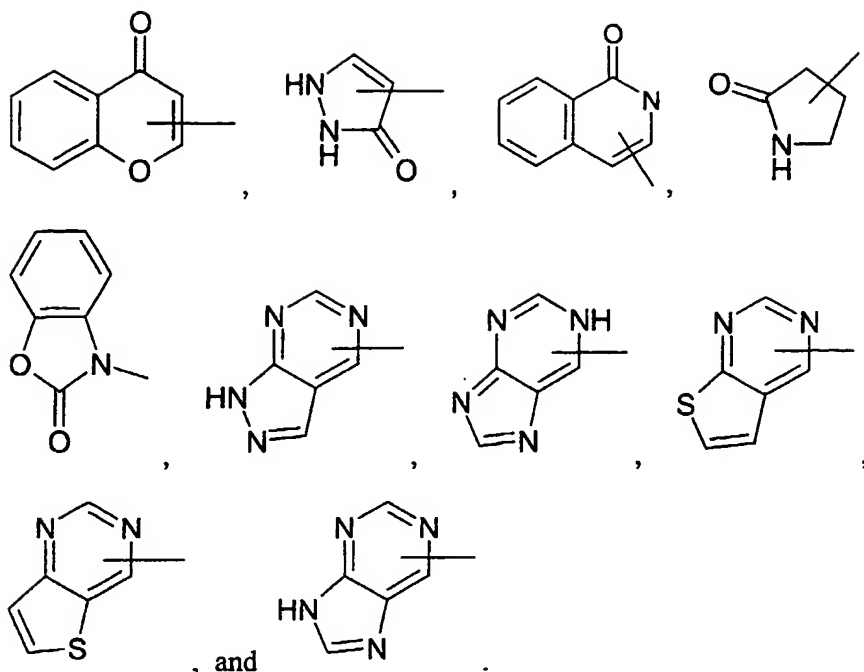
Alkyl may be linear or branched. Examples of alkyl groups/moieties containing up to twelve carbon atoms include methyl, ethyl, n-propyl, iso-propyl, n-butyl, iso-butyl, tert-butyl, n-pentyl, n-hexyl, n-heptyl, n-octyl, n-nonyl, n-decyl, n-undecyl and n-dodecyl groups. A C₁₋₆ hydroxyalkyl group will comprise at least one hydroxyl group (for example

20 one, two or three hydroxyl groups) which may be attached to an internal or terminal carbon

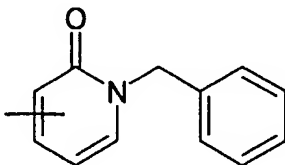
atom of the alkyl chain. Similarly, a carboxy-substituted C₁₋₆ alkoxy group will comprise at least one carboxyl group (for example one, two or three carboxyl groups) which may be attached to an internal or terminal carbon atom of the alkyl chain. A C₁₋₆ haloalkyl or C₁₋₆ haloalkoxy group will comprise at least one halogen atom (for example one, two, three or
5 four halogen atoms independently selected from fluorine, chlorine, bromine and iodine) which may be attached to an internal or terminal carbon atom of the alkyl chain. A halophenyl group will comprise from 1 to 5 halogen atoms independently selected from fluorine, chlorine, bromine and iodine. A C₁₋₆ alkylbenzyl group will comprise at least one C₁₋₆ alkyl group (for example one, two or three C₁₋₆ alkyl groups) attached to the phenyl
10 ring of the benzyl moiety. If there is more than one C₁₋₆ alkyl group attached to the phenyl ring, the groups may be the same or different. In a C₁₋₆ alkoxycarbonylpiperazinyl substituent group, the piperazinyl moiety is attached through a nitrogen atom to the carbonyl moiety. When T represents C(O)NR⁹, it should be understood that the nitrogen atom is attached directly to the six-membered heterocyclic ring in formula (I).

15 The group R¹ may represent a C₁₋₁₂, preferably C₁₋₁₀, more preferably C₁₋₆, alkyl group optionally substituted by one or more (for example one, two, three or four) substituents independently selected from cyano, hydroxyl, C₁₋₆, preferably C₁₋₄, alkoxy, C₁₋₆, preferably C₁₋₄, alkylthio and C₁₋₆ alkoxycarbonyl, preferably C₁₋₄ alkoxycarbonyl.

 The group R¹ may alternatively represent an optionally substituted 3- to 10-
20 membered saturated or unsaturated ring system which optionally comprises one or two ring carbon atoms that form carbonyl groups and which optionally further comprises one, two, three or four ring heteroatoms independently selected from nitrogen, oxygen and sulphur. Examples of ring systems that may be used which can be monocyclic or polycyclic include cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, phenyl, pyrazolyl, furyl, thienyl,
25 imidazolyl, quinolinyl (for example 2-quinolinyl, 3-quinolinyl or 4-quinolinyl), pyridinyl (for example 2-pyridinyl, 3-pyridinyl or 4-pyridinyl), 1,3-benzodioxolyl, thiazolyl, benzimidazolyl, oxadiazolyl (for example 1,2,4-oxadiazolyl), triazolyl (such as 1,2,3-triazolyl or 1,2,4-triazolyl), benzothiazolyl, pyrimidinyl (for example 2-pyrimidinyl or 4-pyrimidinyl), benzothienyl,



- The ring system of R^1 may be optionally substituted by one or more (for example
- 5 one, two, three or four) substituents independently selected from halogen (for example fluorine, chlorine, bromine or iodine); cyano; nitro; hydroxyl; carboxyl; C_{1-6} , preferably C_{1-4} , alkyl (especially methyl or ethyl); C_{1-6} , preferably C_{1-4} , hydroxyalkyl; C_{1-6} , preferably C_{1-4} , haloalkyl (for example trifluoromethyl); C_{1-6} , preferably C_{1-4} , alkoxy (especially methoxy, ethoxy, n-propoxy or isopropoxy); carboxy-substituted C_{1-6} , preferably C_{1-4} ,
- 10 alkoxy; C_{1-6} , preferably C_{1-4} , alkylthio (especially methylthio, ethylthio, n-propylthio and tert-butylthio); C_{1-6} , preferably C_{1-4} , alkylthiomethyl (particularly methylthiomethyl); C_{1-6} , preferably C_{1-4} , alkylcarbonylamino (especially methylcarbonylamino); $-NR^7R^8$; $-C(O)NR^7R^8$; C_{1-6} , preferably C_{1-4} , alkylcarbonyloxymethyl (particularly methylcarbonyloxymethyl); C_{1-6} , preferably C_{1-4} , alkoxycarbonyl (especially methoxycarbonyl or ethoxycarbonyl); C_{1-6} , preferably C_{1-4} , alkoxycarbonylpiperazinyl;
- 15 furyl; phenyl; pyridinyl; pyrazinyl; halophenyl (especially chlorophenyl); thienyl; thienylmethyl; C_{1-6} , preferably C_{1-4} , alkylbenzyl (particularly methylbenzyl); and



The group R^1 may be an aromatic 5-membered heterocyclyl having 2, 3 or 4 ring nitrogen atoms (for example 1,2,4-triazole, 1,2,4-oxadiazole, 1,3,4-oxadiazole or tetrazole) substituted by one heteroaromatic ring (such as pyridine or pyrazole) which is itself optionally substituted by halogen or C_{1-4} alkyl; or R^1 is halophenyl (for example phenyl
 5 optionally substituted (such as in the 4-position) by fluoro or chloro; such as 4-chlorophenyl or 4-fluorophenyl).

The group Q is especially oxygen or m is 0. Alternatively, Q may be a sulphur atom or a group NH, C(O) or NHC(O).

The group n is, for example, 1 or 2.

10 The group T is, for example, NH, C(O)NH or NHC(O)NH; for example T is a NH or C(O)NH group; especially T is C(O)NH.

The groups X^1 , X^2 , X^3 and X^4 are preferably all CH_2 or CHR^{12} , wherein the R^{12} groups of X^1 and X^3 or X^4 , or, X^2 and X^3 or X^4 join to form CH_2CH_2 ; provided always that at least two of X^1 , X^2 , X^3 and X^4 are CH_2 . The groups X^1 , X^2 , X^3 and X^4 are especially all
 15 CH_2 .

It is preferred that each R^2 and R^3 independently represents a hydrogen atom or a methyl group, especially a hydrogen atom.

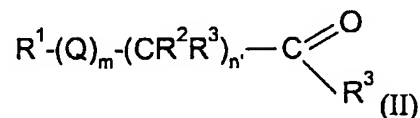
The groups R^4 and R^5 are especially, independently, hydrogen or C_{1-4} alkyl; particularly both hydrogen.

20 The group R^6 is, for example, a phenyl group optionally substituted by one or more (for example one, two, three or four) substituents independently selected from halogen (for example fluorine, chlorine, bromine or iodine), amino, nitro, cyano, sulphonyl, sulphonamido, C_{1-6} , preferably C_{1-4} , alkyl, C_{1-6} , preferably C_{1-4} , haloalkoxy, methylenedioxy or C_{1-6} , preferably C_{1-4} , alkylsulphonyl. The group R^6 is especially phenyl
 25 optionally substituted by halogen or methylenedioxy, particularly R^6 is a phenyl group substituted by halogen. Examples of R^6 include 3-chlorophenyl, 4-chlorophenyl or, especially, 3,4-dichlorophenyl.

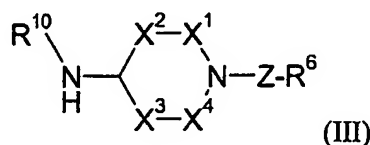
The groups R^7 and R^8 are, for example, hydrogen, C_1-C_6 , preferably C_1-C_4 , hydroxyalkyl, C_{3-6} cycloalkyl (cyclopropyl, cyclobutyl, cyclopentyl or cyclohexyl) or C_{1-6} ,
 30 preferably C_{1-4} , alkyl optionally substituted by phenyl (for example one or two phenyl groups). More preferably, R^7 and R^8 each independently represent hydrogen, C_2 hydroxyalkyl, cyclopropyl or C_{1-2} alkyl optionally substituted by phenyl.

Compounds of formula (I) can be prepared by one of the following methods:

- (a) when n is at least 1, the CR^2R^3 group attached directly to T is CHR^3 and T is NR^{10} , reacting a compound of formula

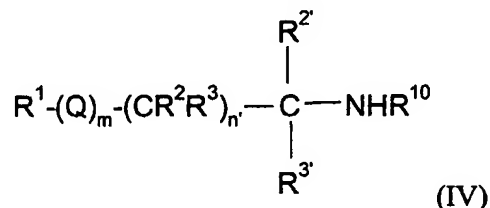


wherein n' is 0 or an integer from 1 to 3 and R^1 , R^2 , R^3 , m and Q are as defined above, with a compound of formula

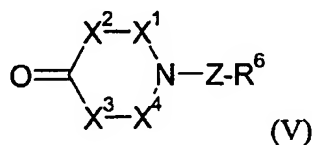


or a salt thereof, wherein X^1 , X^2 , X^3 , X^4 , Z , R^6 and R^{10} are as defined above, in the presence of a reducing agent;

- (b) when n is at least 1, the CR^2R^3 group attached directly to T is $\text{C}(\text{C}_1\text{-C}_4 \text{ alkyl})_2$ and T is NR^{10} , reacting a compound of formula

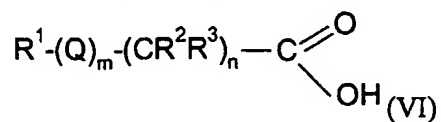


wherein n' is 0 or an integer from 1 to 3, $\text{R}^{2'}$ and $\text{R}^{3'}$ each independently represent a $\text{C}_1\text{-C}_4$ alkyl group, and R^1 , R^2 , R^3 , R^{10} , m and Q are as defined above, with a compound of formula



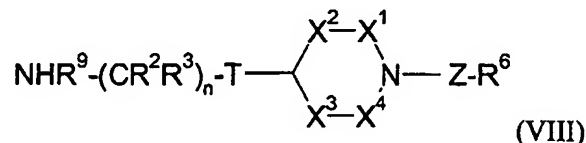
wherein X^1 , X^2 , X^3 , X^4 , Z and R^6 are as defined above, in the presence of a reducing agent;

- (c) when T is $\text{C}(\text{O})\text{NR}^{10}$, reacting a compound of formula



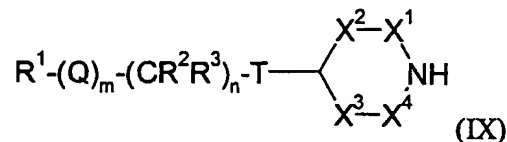
wherein R^1 , R^2 , R^3 , Q , m and n are as defined above, with a compound of formula (III) or a salt thereof as defined in (a) above;

- (d) when m is 1 and Q is NR^9 , reacting a compound of formula (VII), $R^1 - L^1$, wherein L^1 represents a leaving group (for example a halogen atom) and R^1 is as defined above, with a compound of formula



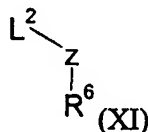
or a salt thereof, wherein n , T , X^1 , X^2 , X^3 , X^4 , Z , R^2 , R^3 , R^6 and R^9 are as defined above;

- (e) when at least one of R^4 and R^5 represents a hydrogen atom, reacting a compound of formula



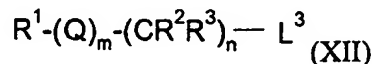
or a salt thereof, wherein R^1 , R^2 , R^3 , Q , m , n , X^1 , X^2 , X^3 , X^4 and T are as defined above, with a compound of general formula (X), $R^6 - C(O) - R^{20}$, wherein R^{20} represents a hydrogen atom or a C_1 - C_4 alkyl group and R^6 is as defined above, in the presence of a reducing agent;

- (f) reacting a compound of formula (IX) as defined in (e) above, with a compound of formula



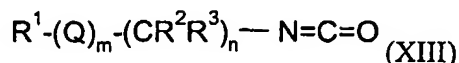
wherein L^2 represents a leaving group (for example a halogen atom) and Z and R^6 are as defined above;

- (g) when T is NR^{10} , reacting a compound of formula



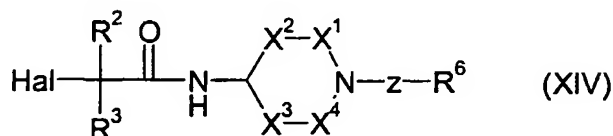
wherein L^3 represents a leaving group (for example a halogen atom) and R^1 , R^2 , R^3 , m , n and Q are as defined above, with a compound of formula (III) or a salt thereof as defined in (a) above;

(h) when T is NHC(O)NR^{10} , reacting a compound of formula



wherein R^1 , R^2 , R^3 , Q, m and n are as defined above, with a compound of formula (III) or a salt thereof as defined in (a) above;

(i) when T is C(O)NH , Z is CH_2 , n is 1, R^2 and R^3 are hydrogen or $\text{C}_1\text{-C}_4$ alkyl and Q is oxygen or sulphur, reacting a compound of formula (XIV):



wherein Hal is a suitable halogen (such as bromo or chloro), R^2 , R^3 , X^1 , X^2 , X^3 , X^4 , Z and R^6 are as defined above, with R^1OH or R^1SH in the presence of a suitable

base (such as potassium carbonate or sodium or potassium hydroxide);

and optionally after (a), (b), (c), (d), (e), (f), (g), (h) or (i) forming a pharmaceutically acceptable salt or solvate of the compound of formula (I) obtained. Compounds of formulae (II) to (XIV) are either commercially available, or are known in the literature or may be prepared using known techniques. The compounds of formula (I) can be isolated from reaction mixtures and purified using standard techniques.

When functional groups such as hydroxyl or amino are present in starting reagents or intermediate compounds they may need to be protected by protecting groups. Thus, the preparation of the compounds of formula (I) may involve, at an appropriate stage, the addition and subsequent removal of one or more protecting groups. The protection and deprotection of functional groups is described in 'Protective Groups in Organic Chemistry', edited by J.W.F. McOmie, Plenum Press (1973) and 'Protective Groups in Organic Synthesis', 2nd edition, T.W. Greene and P.G.M. Wuts, Wiley-Interscience (1991).

The compounds of formula (I) have activity as pharmaceuticals, in particular as modulators of chemokine receptor activity, especially as modulators of the activity of the CCR3 chemokine receptor.

The pharmaceutical combination of the present invention can be used to in the treatment of conditions or diseases in which both antagonism of CCR3 chemokine receptor activity and histamine antagonism, leukotriene modulation, beta-agonism,

phosphodiesterase inhibition or the administration of a steroid, human cytokine or an antibody is beneficial. Examples of these conditions include:

- (1) **(the respiratory tract)** obstructive airways diseases including chronic obstructive pulmonary disease (COPD); asthma, such as bronchial, allergic, intrinsic, extrinsic and dust asthma, particularly chronic or inveterate asthma (for example late asthma and airways hyper-responsiveness); bronchitis; acute, allergic, atrophic rhinitis and chronic rhinitis including rhinitis caseosa, hypertrophic rhinitis, rhinitis purulenta, rhinitis sicca and rhinitis medicamentosa; membranous rhinitis including croupous, fibrinous and pseudomembranous rhinitis and scrofulous rhinitis; seasonal rhinitis including rhinitis nervosa (hay fever) and vasomotor rhinitis; sarcoidosis, farmer's lung and related diseases, fibroid lung and idiopathic interstitial pneumonia;
- (2) **(skin)** psoriasis, atopic dermatitis, contact dermatitis and other eczematous dermatides, seborrhoetic dermatitis, Lichen planus, Pemphigus, bullous Pemphigus, Epidermolysis bullosa, urticaria, angiodermas, vasculitides, erythemas, cutaneous eosinophilias, uveitis, Alopecia areata and conjunctivitis (for example vernal conjunctivitis);
- (3) **(gastrointestinal tract)** Coeliac disease, proctitis, eosinophilic gastro-enteritis, mastocytosis, Crohn's disease, inflammatory bowel disease, irritable bowel syndrome, ulcerative colitis, food-related allergies which have effects remote from the gut, for example, migraine, rhinitis and eczema;
- (4) **(bone and joints)** rheumatoid arthritis, osteoarthritis, seronegative spondyloarthropathies (including ankylosing spondylitis, psoriatic arthritis and Reiter's disease), Behcet's disease, Sjogren's syndrome and systemic sclerosis;
- (5) **(allograft rejection)** acute and chronic following, for example, transplantation of kidney, heart, liver, lung, bone marrow, skin and cornea; and chronic graft versus host disease; and,
- (6) **(other tissues and systemic disease)** multiple sclerosis, atherosclerosis, Acquired Immunodeficiency Syndrome (AIDS), lupus erythematosus, systemic lupus, erythematosus, Hashimoto's thyroiditis, myasthenia gravis, type I diabetes, nephrotic syndrome, eosinophilia fascitis, hyper IgE syndrome, lepromatous leprosy, sezary syndrome and idiopathic thrombocytopenia pupura.

Thus, the present invention provides a pharmaceutical combination as hereinbefore defined for use in therapy.

In a further aspect, the present invention provides the use of a pharmaceutical combination as hereinbefore defined in the manufacture of a medicament for use in
5 therapy.

In the context of the present specification, the term "therapy" also includes "prophylaxis" unless there are specific indications to the contrary. The terms "therapeutic" and "therapeutically" should be construed accordingly.

Prophylaxis is expected to be particularly relevant to the treatment of persons who
10 have suffered a previous episode of, or are otherwise considered to be at increased risk of, the disease or condition in question. Persons at risk of developing a particular disease or condition generally include those having a family history of the disease or condition, or those who have been identified by genetic testing or screening to be particularly susceptible to developing the disease or condition.

In another aspect the present invention provides the use of a pharmaceutical combination as hereinbefore defined in the manufacture of a medicament for the modulation of the CCR3 chemokine receptor and histamine antagonism, leukotriene modulation, beta-agonism, phosphodiesterase inhibition or the administration of a steroid, human cytokine or an antibody is beneficial. In a further aspect such medicament is for the
15 treatment of asthma or rhinitis.

The invention also provides a method of treating asthma or rhinitis in a person suffering from, or at risk of, said disease, which comprises administering to the person a therapeutically effective amount of a pharmaceutical combination as hereinbefore defined.

For the above-mentioned therapeutic uses the dosage administered will, of course,
25 vary with the compound employed, the mode of administration, the treatment desired and the disorder indicated.

The compound of formula (I) and the histamine antagonist, steroid, leukotriene modulator, human cytokine, beta-agonist, phosphodiesterase inhibitor or antibody may be comprised in the same or separate formulations. When in separate formulations, the
30 compound of formula (I) may be administered before, at or about the same time as or after the histamine antagonist, steroid, leukotriene modulator, human cytokine, beta-agonist, phosphodiesterase inhibitor or antibody.

In one further aspect of the invention the compound of formula (I) is administered at or about the same time as the histamine antagonist, steroid, leukotriene modulator, human cytokine, beta-agonist, phosphodiesterase inhibitor or antibody. Especially, the compound of formula (I) and the histamine antagonist, steroid, leukotriene modulator, human cytokine, beta-agonist, phosphodiesterase inhibitor or antibody. Further, said formulation is designed for oral administration.

In a further aspect the present invention provides a pharmaceutical composition comprising a compound of formula (I) and a histamine antagonist, steroid, leukotriene modulator, human cytokine, beta-agonist, phosphodiesterase inhibitor or antibody and a pharmaceutically acceptable adjuvant, diluent or carrier. Depending on the mode of administration, the pharmaceutical composition will preferably comprise from 0.05 to 99%w (per cent by weight), more preferably from 0.05 to 80%w, still more preferably from 0.10 to 70%w, and even more preferably from 0.10 to 50%w, of active ingredients, all percentages by weight being based on total composition.

The pharmaceutical composition may be administered topically (for example to the lung and/or airways or to the skin) in the form of a solution, suspension, heptafluoroalkane aerosol or dry powder formulation; or systemically, for example by oral administration in the form of a tablet, capsule, syrup, powder, aerosol or granule, or by parenteral administration in the form of a solution or suspension, or by subcutaneous administration or by rectal administration in the form of a suppository or transdermally.

The combination may be formulated as a tablet which may include a diluent such as microcrystalline cellulose or lactose monohydrate, a binder such as polyvinylpyrrolidone or hydroxypropylmethylcellulose, a disintegrant such as crospovidone or starch, a glidant such as talc or fumed silica and a lubricant such as magnesium stearate or sodium stearyl fumarate. Optionally, an excipient to control the release rate of the active compounds, such as hydroxypropylmethylcellulose or polymethylmethacrylate derivatives, may be included.

Alternatively, the formulation may be presented as a capsule with either a gelatin, starch or hydroxypropylmethylcellulose shell and a fill formulation comprising the active ingredients and a diluent such as microcrystalline cellulose or lactose monohydrate, a binder such as polyvinylpyrrolidone or hydroxypropylmethylcellulose, a disintegrant such as crospovidone or starch, a glidant such as talc or fumed silica, and a lubricant such as

magnesium stearate or sodium stearyl fumarate. Optionally, an excipient to control the release rate of the active compounds, such as hydroxypropylmethylcellulose or polymethylmethacrylate derivatives, may be included.

Parenteral dosage forms may be prepared using an aqueous or organic vehicle, such as oils, alcohols, propylene glycol, polyethylene glycol or other pharmaceutically acceptable solvent, solubilisers such as polyethylene oxide - polypropylene oxide block copolymers or polysorbates, tonicity modifiers such as sodium chloride or dextrose, stabilisers such as antioxidants or chelating agents, and pH modifiers and buffers such as sodium hydroxide or sodium borate.

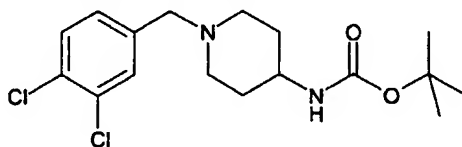
Oral dosage forms can be prepared by tableting or encapsulation of blends produced by wet granulation, dry granulation, print deposition, direct powder blending or other pharmaceutically acceptable process.

Parenteral dosage forms may be prepared by processes such as preparation of a solution, colloid, suspension or emulsion which is then sterilised, by processes such as filtration, autoclaving or irradiation. The dosage form may also be presented as a lyophilised solid for reconstitution.

The following Examples illustrate processes by which compounds of formula (I) can be prepared.

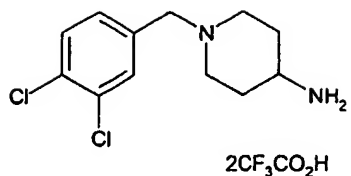
EXAMPLE A

Preparation of 1-(3,4-dichlorobenzyl)-4-piperidinamine, di-trifluoroacetate salt
Step i: tert-butyl 1-(3,4-dichlorobenzyl)-4-piperidinylcarbamate



Sodium triacetoxyborohydride (6g) was added to a stirred solution of 3,4-dichlorobenzaldehyde (4.2g) and 1,1-dimethylethyl-4-piperidinyl carbamate (4g) in dichloromethane (50ml). The mixture was stirred at room temperature for 4h then partitioned between ethyl acetate and aqueous sodium hydrogencarbonate. The organic layer was washed with water, dried and evaporated under reduced pressure. The residue was triturated with ether to give a white solid (3.5g) which was used directly in step ii.

Step ii: 1-(3,4-Dichlorobenzyl)-4-piperidinamine, di-trifluoroacetate salt



The product from step (i) (3.5g) was treated with trifluoroacetic acid (10ml) in dichloromethane (40ml). After 72h, the solution was evaporated, the residue triturated with ether and the solid (4.3g) collected.

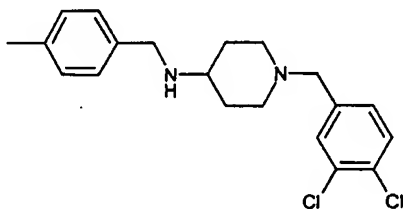
5

Examples 1-47

1-(3,4-Dichlorobenzyl)-4-piperidinamine, di-trifluoroacetate salt (2mg), the appropriate aldehyde (2 equivalents), sodium triacetoxyborohydride (3 equivalents) and diisopropylethylamine (2 equivalents) in acetonitrile (0.08ml) and 1-methyl-2-pyrrolidinone (0.12ml) were left at room temperature for 24h. The reaction mixture was
 10 evaporated to dryness and the residue dissolved in dimethylsulphoxide (0.4ml).

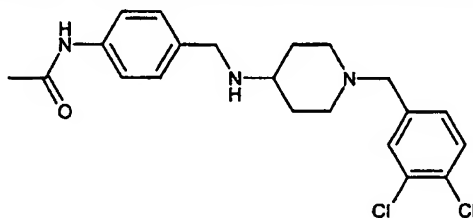
Example 1

N-[1-(3,4-Dichlorobenzyl)-4-piperidinyl]-N-(4-methylbenzyl)amine



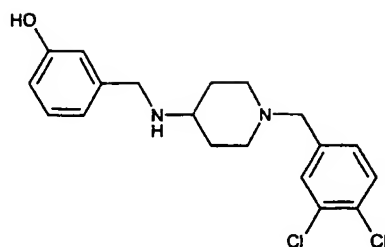
Example 2

15 N-[4-({[1-(3,4-Dichlorobenzyl)-4-piperidinyl]amino}methyl)phenyl]acetamide



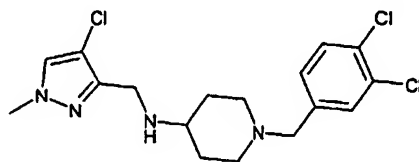
Example 3

3-({[1-(3,4-Dichlorobenzyl)-4-piperidinyl]amino}methyl)phenol



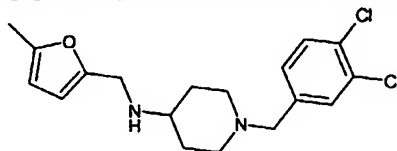
Example 4

N-[(4-Chloro-1-methyl-1H-pyrazol-3-yl)methyl]-1-(3,4-dichlorobenzyl)-4-piperidinamine



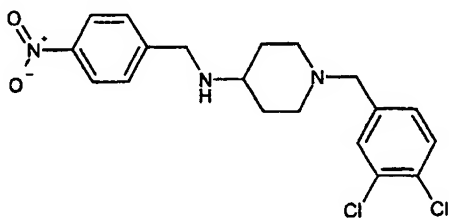
Example 5

N-[1-(3,4-Dichlorobenzyl)-4-piperidinyl]-N-[(5-methyl-2-furyl)methyl]amine



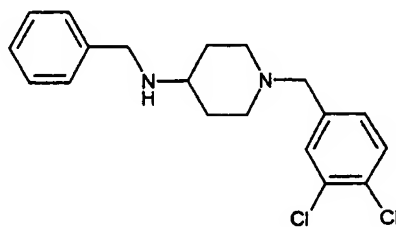
Example 6

N-[1-(3,4-Dichlorobenzyl)-4-piperidinyl]-N-(4-nitrobenzyl)amine



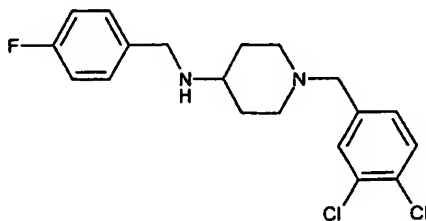
Example 7

N-Benzyl-1-(3,4-dichlorobenzyl)-4-piperidinamine

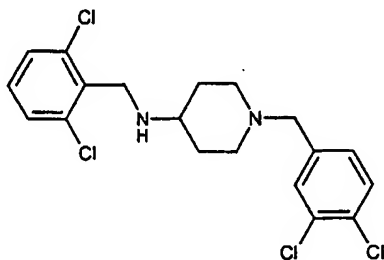


Example 8

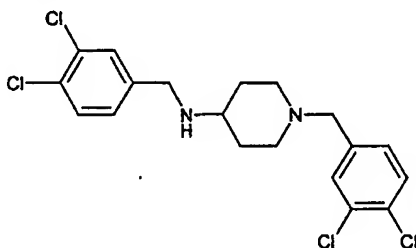
N-[1-(3,4-Dichlorobenzyl)-4-piperidiny]-N-(4-fluorobenzyl)amine

Example 9

5 N-(2,6-Dichlorobenzyl)-1-(3,4-dichlorobenzyl)-4-piperidinamine

Example 10

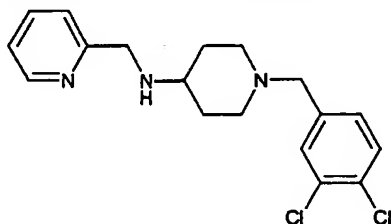
N,1-Bis(3,4-dichlorobenzyl)-4-piperidinamine



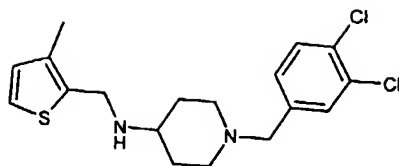
10

Example 11

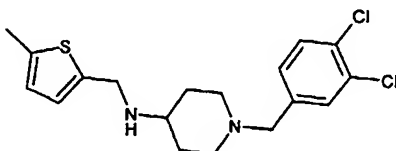
N-[1-(3,4-Dichlorobenzyl)-4-piperidiny]-N-(2-pyridinylmethyl)amine

Example 12

N-[1-(3,4-Dichlorobenzyl)-4-piperidiny]-N-[(3-methyl-2-thienyl)methyl]amine

Example 13

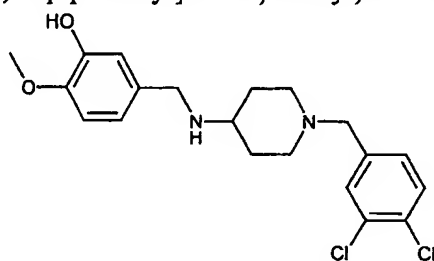
N-[1-(3,4-Dichlorobenzyl)-4-piperidiny]-N-[(5-methyl-2-thienyl)methyl]amine



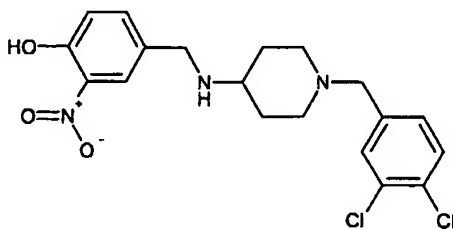
5

Example 14

5-([1-(3,4-Dichlorobenzyl)-4-piperidiny]amino)methyl)-2-methoxyphenol

Example 15

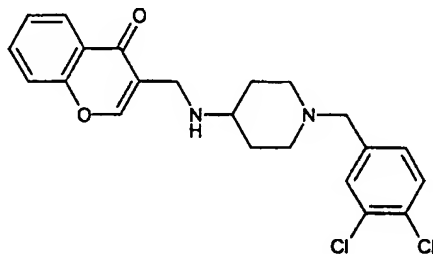
4-([1-(3,4-Dichlorobenzyl)-4-piperidiny]amino)methyl)-2-nitrophenol



10

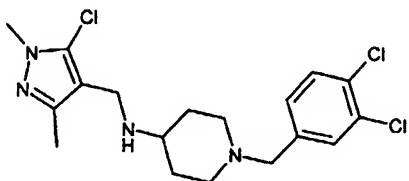
Example 16

3-([1-(3,4-Dichlorobenzyl)-4-piperidiny]amino)methyl)-4H-chromen-4-one



Example 17

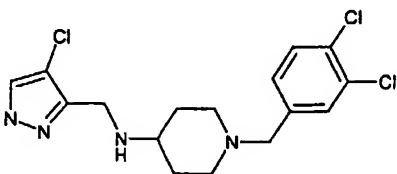
N-[(5-Chloro-1,3-dimethyl-1H-pyrazol-4-yl)methyl]-1-(3,4-dichlorobenzyl)-4-piperidinamine



5

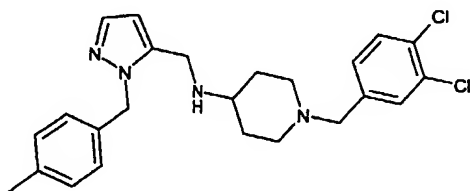
Example 18

N-[(4-Chloro-1H-pyrazol-3-yl)methyl]-1-(3,4-dichlorobenzyl)-4-piperidinamine

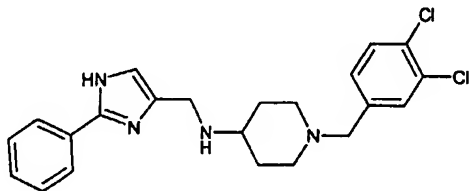
Example 19

N-[1-(3,4-Dichlorobenzyl)-4-piperidinyl]-N-[[1-(4-methylbenzyl)-1H-pyrazol-5-yl]methyl]amine

10

Example 20

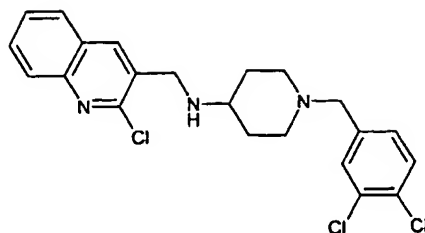
N-[1-(3,4-Dichlorobenzyl)-4-piperidinyl]-N-[(2-phenyl-1H-imidazol-4-yl)methyl]amine



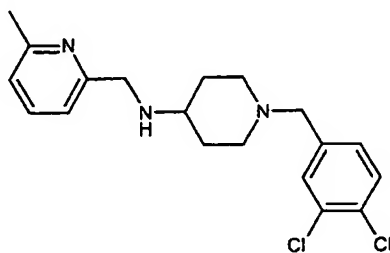
15

Example 21

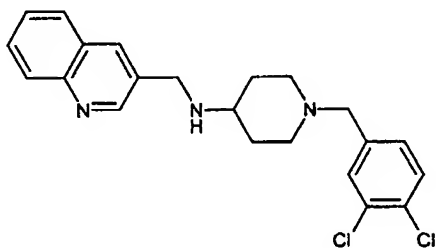
N-[(2-Chloro-3-quinolinyl)methyl]-1-(3,4-dichlorobenzyl)-4-piperidinamine

Example 22

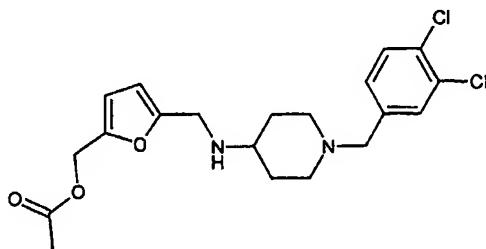
N-[1-(3,4-Dichlorobenzyl)-4-piperidinyl]-N-[(6-methyl-2-pyridinyl)methyl]amine

Example 23

N-[1-(3,4-Dichlorobenzyl)-4-piperidinyl]-N-(3-quinolinylmethyl)amine

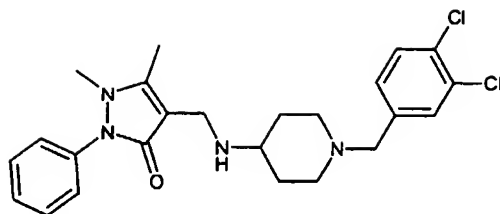
Example 24

[5-({[1-(3,4-Dichlorobenzyl)-4-piperidinyl]amino}methyl)-2-furyl]methyl acetate

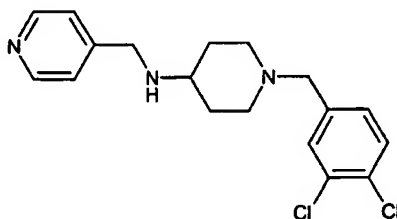
Example 25

4-({[1-(3,4-Dichlorobenzyl)-4-piperidinyl]amino}methyl)-1,5-dimethyl-2-phenyl-1,2-dihydro-3H-pyrazol-3-one

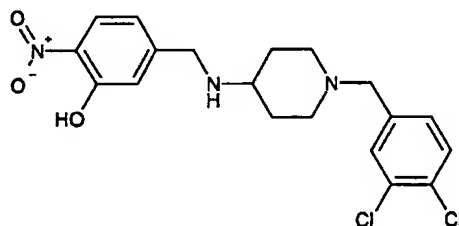
23

Example 26

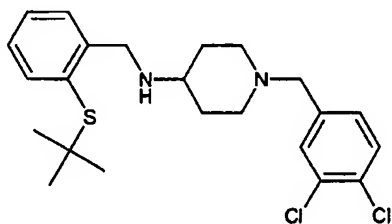
N-[1-(3,4-Dichlorobenzyl)-4-piperidinyl]-N-(4-pyridinylmethyl)amine

Example 27

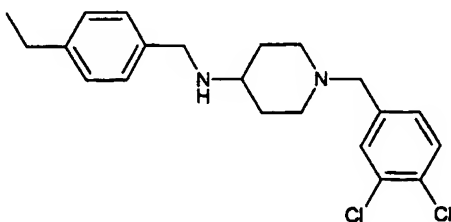
5-({[1-(3,4-Dichlorobenzyl)-4-piperidinyl]amino}methyl)-2-nitrophenol

Example 28

N-[2-(tert-Butylsulfanyl)benzyl]-1-(3,4-dichlorobenzyl)-4-piperidinamine

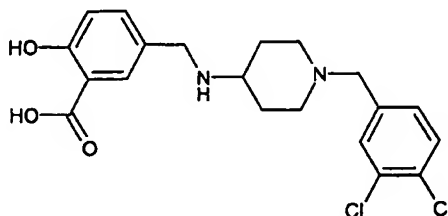
Example 29

N-[1-(3,4-Dichlorobenzyl)-4-piperidinyl]-N-(4-ethylbenzyl)amine

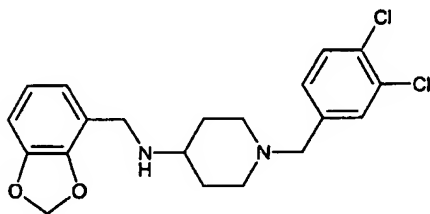


Example 30

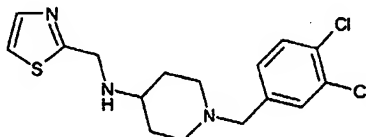
5-({[1-(3,4-Dichlorobenzyl)-4-piperidinyl]amino}methyl)-2-hydroxybenzoic acid

Example 31

5 N-(1,3-Benzodioxol-4-ylmethyl)-1-(3,4-dichlorobenzyl)-4-piperidinamine

Example 32

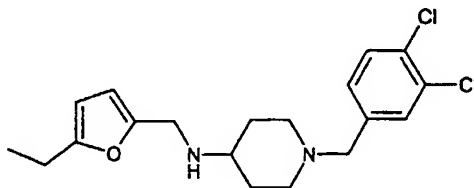
N-[1-(3,4-Dichlorobenzyl)-4-piperidinyl]-N-(1,3-thiazol-2-ylmethyl)amine



10

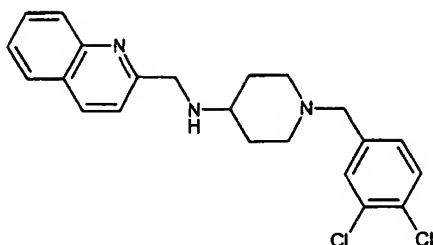
Example 33

N-[1-(3,4-Dichlorobenzyl)-4-piperidinyl]-N-[(5-ethyl-2-furyl)methyl]amine

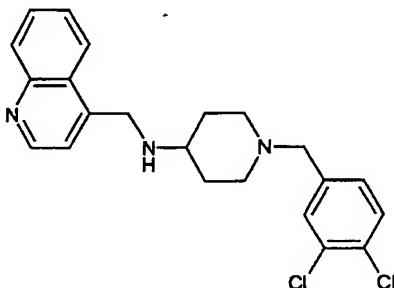
Example 34

N-[1-(3,4-Dichlorobenzyl)-4-piperidinyl]-N-(2-quinolinylmethyl)amine

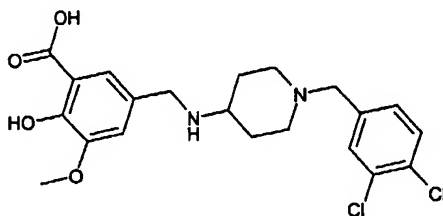
25

Example 35

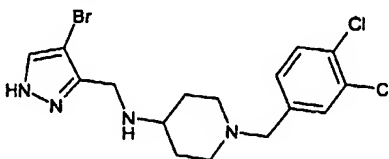
N-[1-(3,4-Dichlorobenzyl)-4-piperidinyl]-N-(4-quinolinylmethyl)amine

Example 36

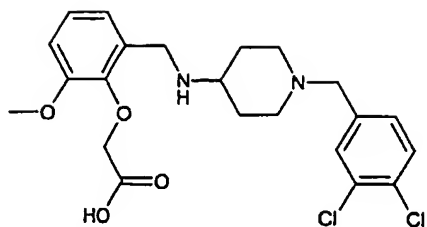
5-([1-(3,4-Dichlorobenzyl)-4-piperidinylamino]methyl)-2-hydroxy-3-methoxybenzoic acid

Example 37

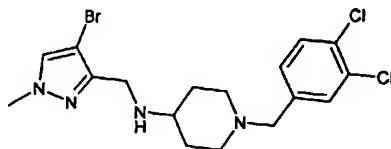
10 N-[(4-Bromo-1H-pyrazol-3-yl)methyl]-1-(3,4-dichlorobenzyl)-4-piperidinamine

Example 38

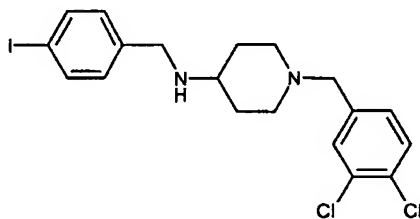
2-[2-([1-(3,4-Dichlorobenzyl)-4-piperidinylamino]methyl)-6-methoxyphenoxy]acetic acid

Example 39

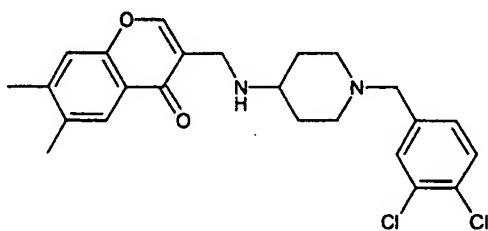
N-[(4-Bromo-1-methyl-1H-pyrazol-3-yl)methyl]-1-(3,4-dichlorobenzyl)-4-piperidinamine

Example 40

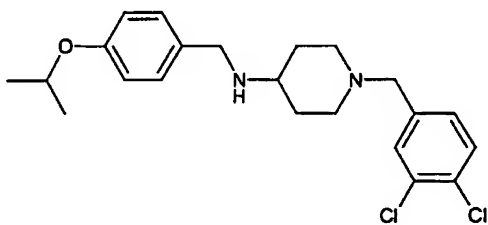
N-[1-(3,4-Dichlorobenzyl)-4-piperidinyl]-N-(4-iodobenzyl)amine

Example 41

3-({[1-(3,4-Dichlorobenzyl)-4-piperidinyl]amino}methyl)-6,7-dimethyl-4H-chromen-4-one

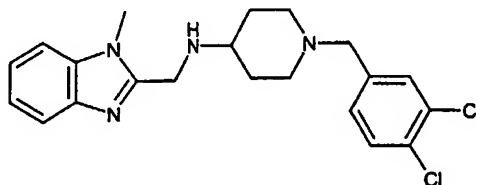
Example 42

N-[1-(3,4-Dichlorobenzyl)-4-piperidinyl]-N-(4-isopropoxybenzyl)amine



Example 43

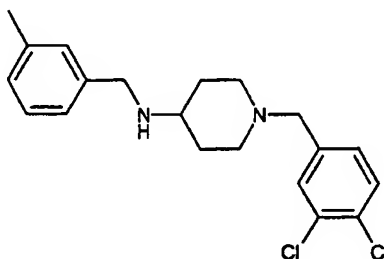
N-[1-(3,4-Dichlorobenzyl)-4-piperidiny]-N-[(1-methyl-1H-benzimidazol-2-yl)methyl]amine



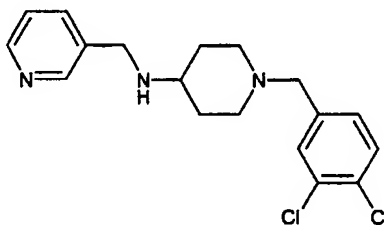
5

Example 44

N-[1-(3,4-Dichlorobenzyl)-4-piperidiny]-N-(3-methylbenzyl)amine

Example 45

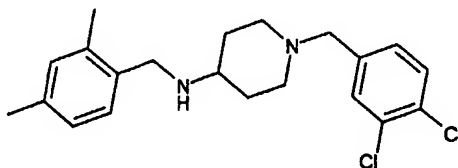
N-[1-(3,4-Dichlorobenzyl)-4-piperidiny]-N-(3-pyridinylmethyl)amine



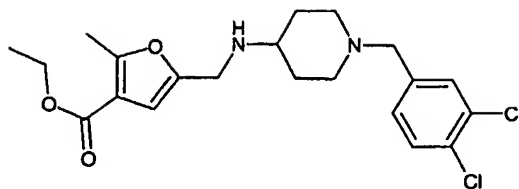
10

Example 46

N-[1-(3,4-Dichlorobenzyl)-4-piperidiny]-N-(2,4-dimethylbenzyl)amine

Example 47

15 Ethyl 5-({[1-(3,4-dichlorobenzyl)-4-piperidiny]amino}methyl)-2-methyl-3-furoate

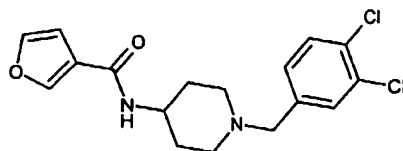


Examples 48-73

Bromo-tris-pyrrolidino-phosphonium hexafluorophosphate (2 equiv) was added to a solution of 1-(3,4-dichlorobenzyl)-4-piperidinamine, di-hydrochloride salt (1mg), the appropriate acid (2 equivalents) and diisopropylethylamine (5 equivalents) in dimethylformamide (0.17ml) and was left at room temperature for 24h. The reaction mixture was evaporated to dryness and the residue dissolved in dimethylsulphoxide (0.3ml).

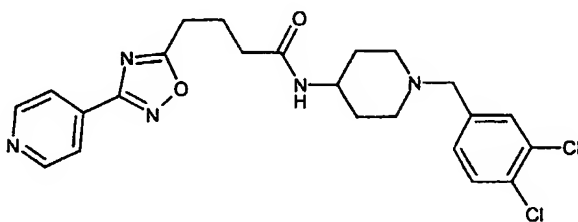
Example 48

10 N-[1-(3,4-Dichlorobenzyl)-4-piperidinyl]-3-furamide



Example 49

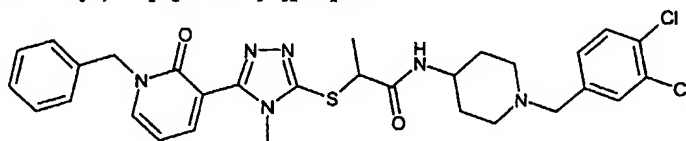
N-[1-(3,4-Dichlorobenzyl)-4-piperidinyl]-4-[3-(4-pyridinyl)-1,2,4-oxadiazol-5-yl]butanamide



15

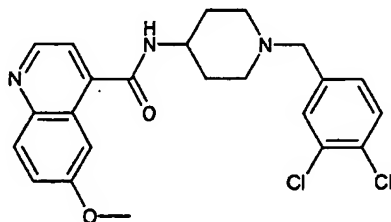
Example 50

2-[[5-(1-Benzyl-2-oxo-1,2-dihydro-3-pyridinyl)-4-methyl-4H-1,2,4-triazol-3-yl]sulfanyl]-N-[1-(3,4-dichlorobenzyl)-4-piperidinyl]propanamide

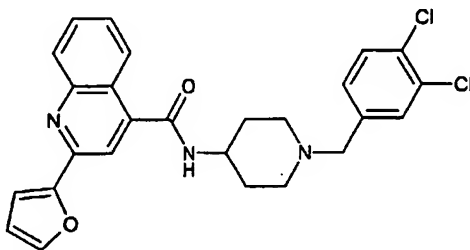


Example 51

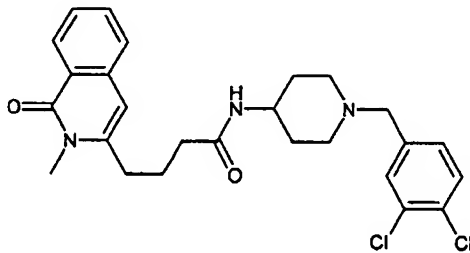
N-[1-(3,4-Dichlorobenzyl)-4-piperidiny]-6-methoxy-4-quinolinecarboxamide

Example 52

5 N-[1-(3,4-Dichlorobenzyl)-4-piperidiny]-2-(2-furyl)-4-quinolinecarboxamide

Example 53

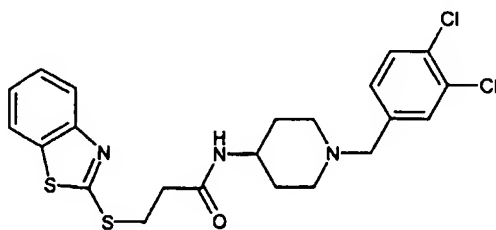
N-[1-(3,4-Dichlorobenzyl)-4-piperidiny]-4-(2-methyl-1-oxo-1,2-dihydro-3-isoquinoliny)butanamide



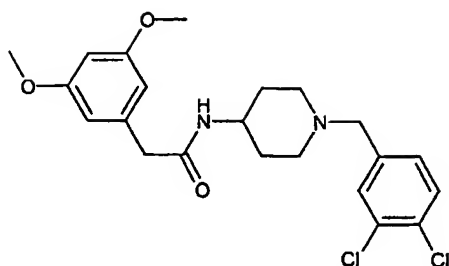
10

Example 54

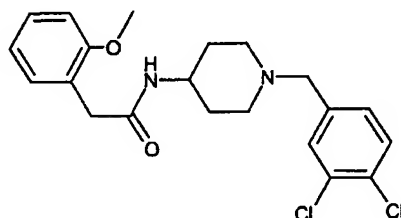
3-(1,3-Benzothiazol-2-ylsulfany)-N-[1-(3,4-dichlorobenzyl)-4-piperidiny]propanamide

Example 55

15 N-[1-(3,4-Dichlorobenzyl)-4-piperidiny]-2-(3,5-dimethoxyphenyl)acetamide

Example 56

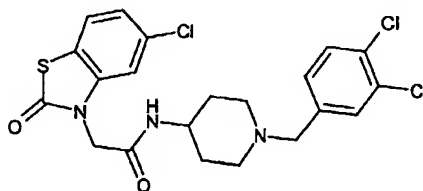
N-[1-(3,4-Dichlorobenzyl)-4-piperidinyl]-2-(2-methoxyphenyl)acetamide



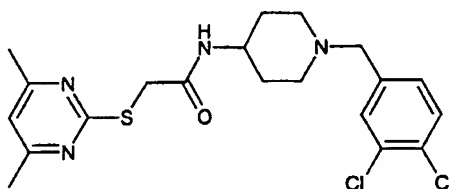
5

Example 57

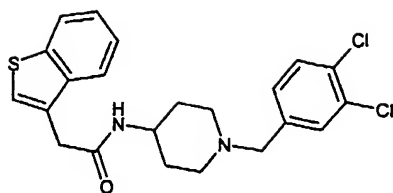
2-[5-Chloro-2-oxo-1,3-benzothiazol-3(2H)-yl]-N-[1-(3,4-dichlorobenzyl)-4-piperidinyl]acetamide

Example 58

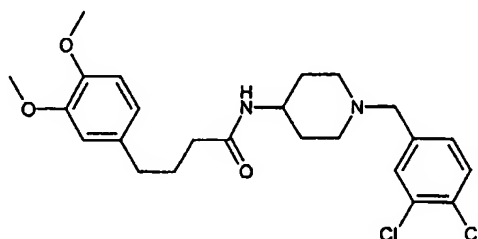
10 N-[1-(3,4-Dichlorobenzyl)-4-piperidinyl]-2-[(4,6-dimethyl-2-pyrimidinyl)sulfanyl]acetamide

Example 59

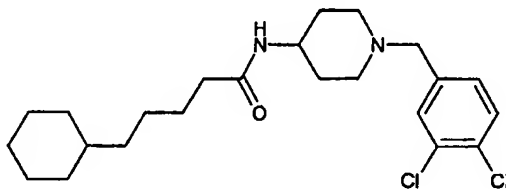
2-(1-Benzothiophen-3-yl)-N-[1-(3,4-dichlorobenzyl)-4-piperidinyl]acetamide

Example 60

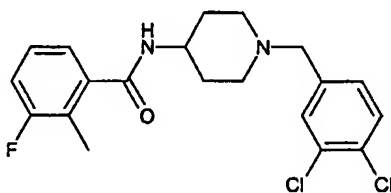
N-[1-(3,4-Dichlorobenzyl)-4-piperidinyl]-4-(3,4-dimethoxyphenyl)butanamide

Example 61

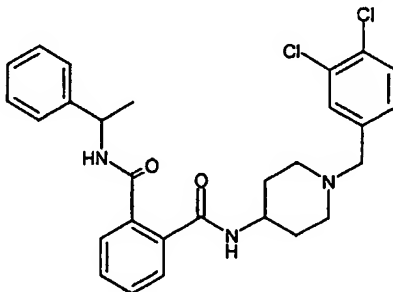
5-Cyclohexyl-N-[1-(3,4-dichlorobenzyl)-4-piperidinyl]pentanamide

Example 62

N-[1-(3,4-Dichlorobenzyl)-4-piperidinyl]-3-fluoro-2-methylbenzamide

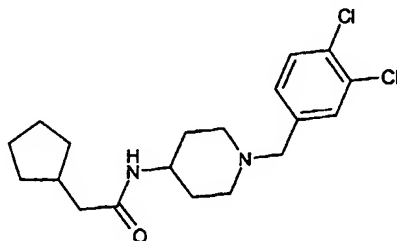
Example 63

N¹-[1-(3,4-Dichlorobenzyl)-4-piperidinyl]-N²-(1-phenylethyl)phthalamide

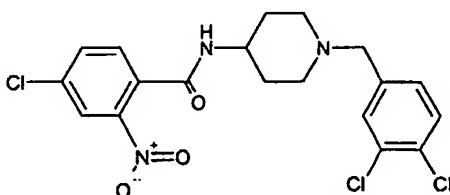


Example 64

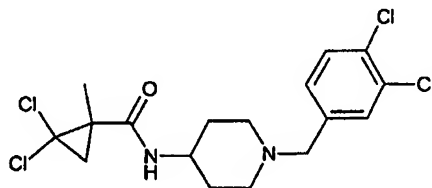
2-Cyclopentyl-N-[1-(3,4-dichlorobenzyl)-4-piperidinyl]acetamide

Example 65

5 4-Chloro-N-[1-(3,4-dichlorobenzyl)-4-piperidinyl]-2-nitrobenzamide

Example 66

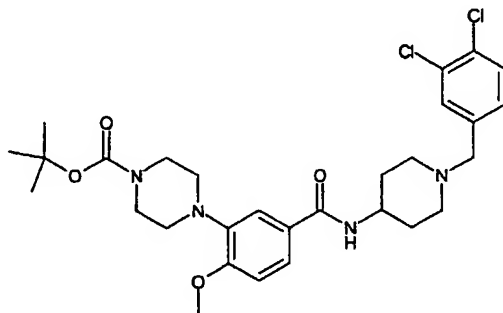
2,2-Dichloro-N-[1-(3,4-dichlorobenzyl)-4-piperidinyl]-1-methylcyclopropanecarboxamide



10

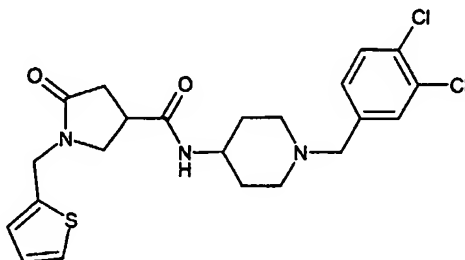
Example 67

tert-Butyl 4-[5-({[1-(3,4-dichlorobenzyl)-4-piperidinyl]amino} carbonyl)-2-methoxyphenyl]-1-piperazinecarboxylate



Example 68

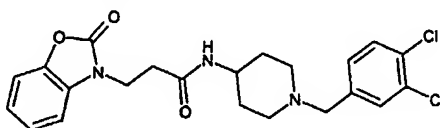
N-[1-(3,4-Dichlorobenzyl)-4-piperidiny]-5-oxo-1-(2-thienylmethyl)-3-pyrrolidinecarboxamide



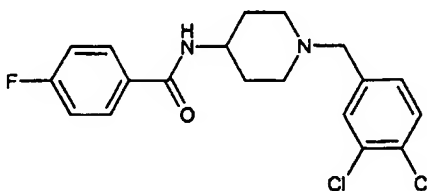
5

Example 69

N-[1-(3,4-Dichlorobenzyl)-4-piperidiny]-3-[2-oxo-1,3-benzoxazol-3(2H)-yl]propanamide

Example 70

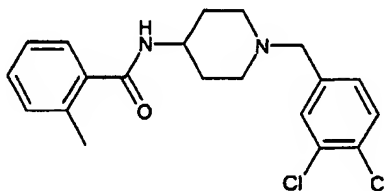
N-[1-(3,4-Dichlorobenzyl)-4-piperidiny]-4-fluorobenzamide



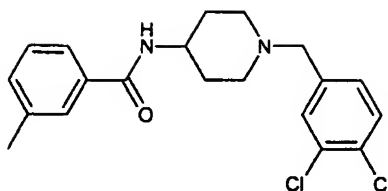
10

Example 71

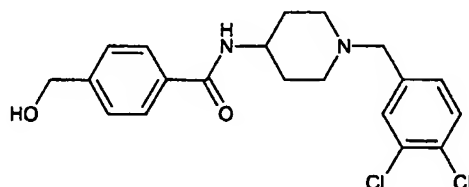
N-[1-(3,4-Dichlorobenzyl)-4-piperidiny]-2-methylbenzamide

Example 72

15 N-[1-(3,4-Dichlorobenzyl)-4-piperidiny]-3-methylbenzamide

Example 73

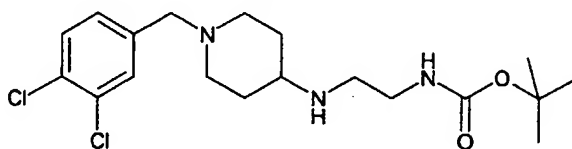
N-[1-(3,4-Dichlorobenzyl)-4-piperidinyl]-4-(hydroxymethyl)benzamide

Examples 74-93

Step i: 1-(3,4-Dichlorobenzyl)-4-piperidinone

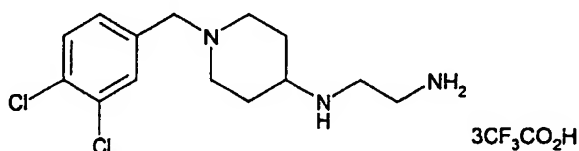
A solution of 3,4-dichlorobenzyl chloride (2.8ml), 4-ketopiperidine hydrochloride monohydrate and triethylamine (8ml) in dimethylformamide (30ml) was stirred at room temperature for 20h. The mixture was partitioned between water and ethyl acetate, the organic layer dried and evaporated under reduced pressure. Purification was by chromatography eluting with 40-50% ethyl acetate/isohexane. Yield 2.1g.

Step ii: tert-Butyl 2-{[1-(3,4-dichlorobenzyl)-4-piperidinyl]amino} ethylcarbamate



A solution of the product from step (i) (1.61g), N-(tert-butoxycarbonyl)-ethylenediamine (1g) and sodium triacetoxyborohydride (2.12g) in dichloromethane (20ml) was stirred at room temperature for 3h. The mixture was partitioned between water and ethyl acetate, the organic layer dried and evaporated under reduced pressure. Yield 1.28g.

Step iii: N-1-[1-(3,4-Dichlorobenzyl)-4-piperidinyl]-1,2-ethanediamine, tri-trifluoroacetate salt



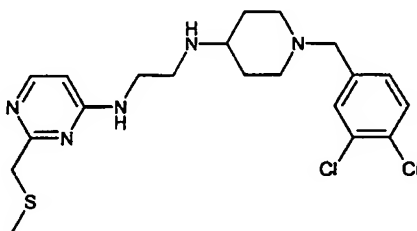
The product from step (ii) (1.28g) was treated with trifluoroacetic acid (5ml) in dichloromethane (10ml). After 20h, the solution was evaporated, the residue triturated with ether and the solid (1.62g) collected.

Step iv: Examples 74-93

- 5 The product from step (iii) (0.0026g), the appropriate activated halo-aromatic (1.25 equivalents) and diisopropylethylamine (10 equivalents) in 1-methyl-2-pyrrolidinone (0.15ml) was heated at 100°C for 20h. The reaction mixture was evaporated to dryness and the residue dissolved in dimethylsulphoxide (0.4ml).

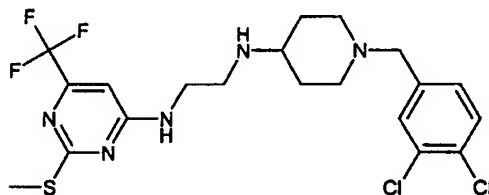
Example 74

- 10 N^1 -[1-(3,4-Dichlorobenzyl)-4-piperidinyl]- N^2 -{2-[(methylsulfonyl)methyl]-4-pyrimidinyl}-1,2-ethanediamine



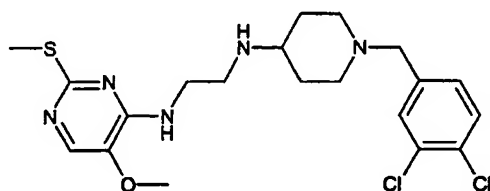
Example 75

- 15 N^1 -[1-(3,4-Dichlorobenzyl)-4-piperidinyl]- N^2 -[2-(methylsulfonyl)-6-(trifluoromethyl)-4-pyrimidinyl]-1,2-ethanediamine



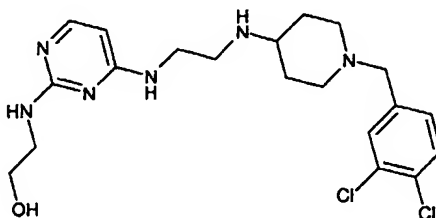
Example 76

- N^1 -[1-(3,4-Dichlorobenzyl)-4-piperidinyl]- N^2 -[5-methoxy-2-(methylsulfonyl)-4-pyrimidinyl]-1,2-ethanediamine

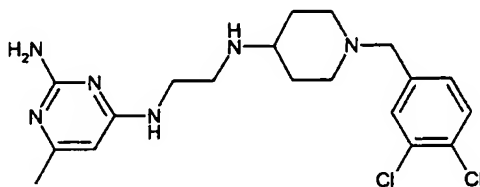


Example 77

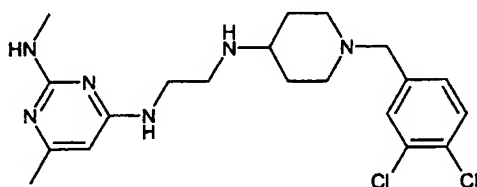
2-({4-[(2-{[1-(3,4-Dichlorobenzyl)-4-piperidinyl]amino}ethyl)amino]-2-pyrimidinyl}amino)-1-ethanol

Example 78

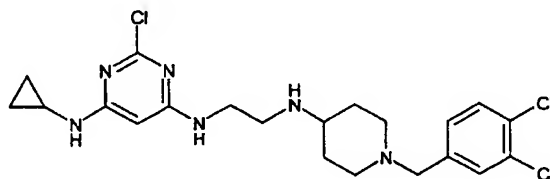
N⁴-(2-{[1-(3,4-Dichlorobenzyl)-4-piperidinyl]amino}ethyl)-6-methyl-2,4-pyrimidinediamine

Example 79

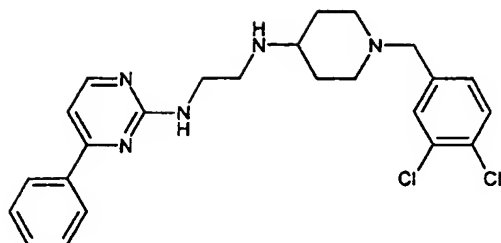
10 N⁴-(2-{[1-(3,4-Dichlorobenzyl)-4-piperidinyl]amino}ethyl)-N²,6-dimethyl-2,4-pyrimidinediamine

Example 80

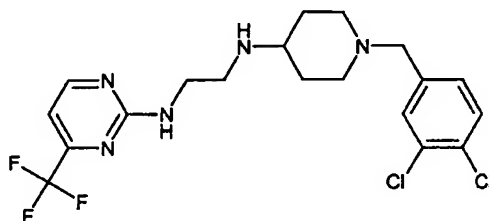
15 2-Chloro-N⁴-cyclopropyl-N⁶-(2-{[1-(3,4-dichlorobenzyl)-4-piperidinyl]amino}ethyl)-4,6-pyrimidinediamine

Example 81

N¹-[1-(3,4-Dichlorobenzyl)-4-piperidinyl]-N²-(4-phenyl-2-pyrimidinyl)-1,2-ethanediamine

**Example 82**

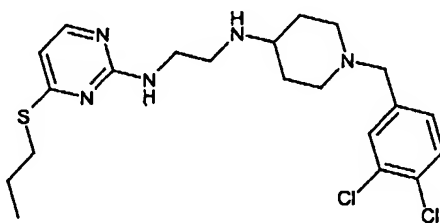
N¹-[1-(3,4-Dichlorobenzyl)-4-piperidinyl]-N²-[4-(trifluoromethyl)-2-pyrimidinyl]-1,2-ethanediamine



5

Example 83

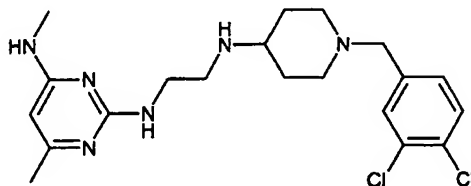
N¹-[1-(3,4-Dichlorobenzyl)-4-piperidinyl]-N²-[4-(propylsulfanyl)-2-pyrimidinyl]-1,2-ethanediamine



10

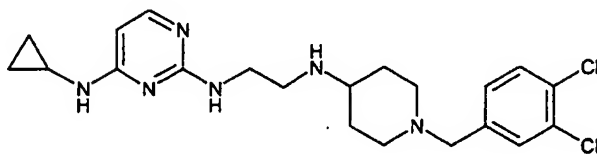
Example 84

N²-(2-{{1-(3,4-Dichlorobenzyl)-4-piperidinyl}amino}ethyl)-N⁴,6-dimethyl-2,4-pyrimidinediamine

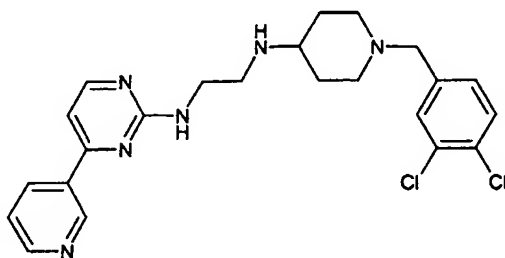


Example 85

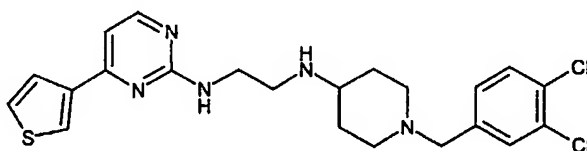
N⁴-Cyclopropyl-N²-(2-{[1-(3,4-dichlorobenzyl)-4-piperidiny]amino}ethyl)-2,4-pyrimidinediamine

Example 86

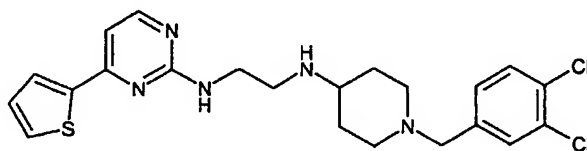
N¹-[1-(3,4-Dichlorobenzyl)-4-piperidiny]-N²-[4-(3-pyridinyl)-2-pyrimidinyl]-1,2-ethanediamine

Example 87

N¹-[1-(3,4-Dichlorobenzyl)-4-piperidiny]-N²-[4-(3-thienyl)-2-pyrimidinyl]-1,2-ethanediamine

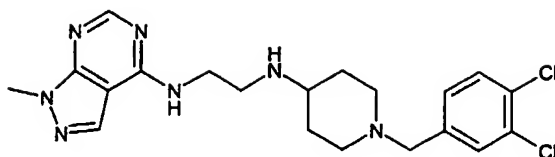
Example 88

N¹-[1-(3,4-Dichlorobenzyl)-4-piperidiny]-N²-[4-(2-thienyl)-2-pyrimidinyl]-1,2-ethanediamine

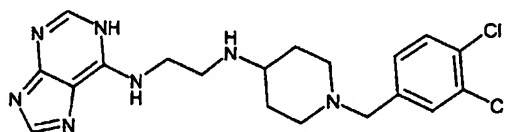
Example 89

N¹-[1-(3,4-Dichlorobenzyl)-4-piperidiny]-N²-(1-methyl-1H-pyrazolo[3,4-d]pyrimidin-4-yl)-1,2-ethanediamine

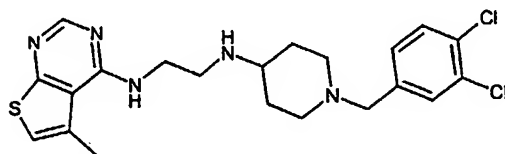
39

Example 90

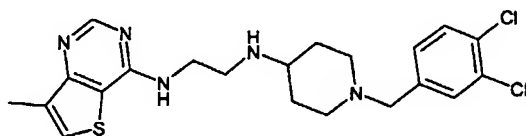
N¹-[1-(3,4-Dichlorobenzyl)-4-piperidinyl]-N²-(1H-purin-6-yl)-1,2-ethanediamine

Example 91

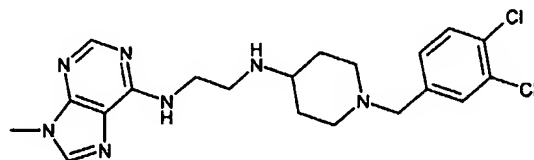
N¹-[1-(3,4-Dichlorobenzyl)-4-piperidinyl]-N²-(5-methylthieno[2,3-d]pyrimidin-4-yl)-1,2-ethanediamine

Example 92

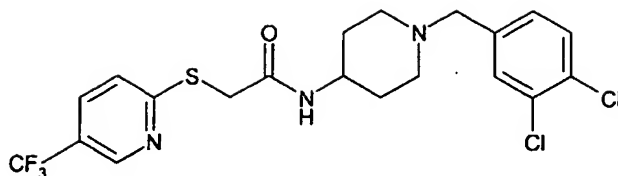
N¹-[1-(3,4-Dichlorobenzyl)-4-piperidinyl]-N²-(7-methylthieno[3,2-d]pyrimidin-4-yl)-1,2-ethanediamine

Example 93

N¹-[1-(3,4-Dichlorobenzyl)-4-piperidinyl]-N²-(9-methyl-9H-purin-6-yl)-1,2-ethanediamine

Example 94

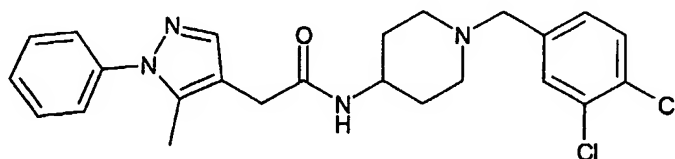
N-[1-(3,4-Dichlorobenzyl)-4-piperidinyl]-2-[[5-(trifluoromethyl)-2-pyridinyl]sulfanyl]acetamide



Carbonyldiimidazole (0.105g) was added to a stirred solution of 2-[(5-(trifluoromethyl)-2-pyridinyl)sulfonyl]acetic acid (0.166g) in dimethylformamide (2ml). After 1h a solution of the product from 1-(3,4-dichlorobenzyl)-4-piperidinamine, di-trifluoroacetate salt (0.3g) in a solution of dimethylformamide and diisopropylethylamine (2 equivalents) (1.5ml) was added and stirred at room temperature for 2h. The mixture was partitioned between water and ethyl acetate, the organic layer washed with water, dried and evaporated under reduced pressure. The residue was triturated with ether and collected. Yield 0.084g as a solid; MP: 98°C.

Example 95

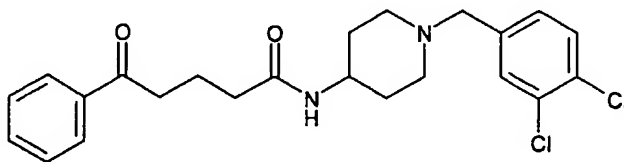
N-[1-(3,4-Dichlorobenzyl)-4-piperidinyl]-2-(5-methyl-1-phenyl-1H-pyrazol-4-yl)acetamide



The title compound was prepared from the product of 1-(3,4-dichlorobenzyl)-4-piperidinamine, di-trifluoroacetate salt (0.3g) and of 2-(5-methyl-1-phenyl-1H-pyrazol-4-yl)acetic acid (0.151g) using the method of Example 94. Yield 0.18g as a solid MP: 165°C.

Example 96

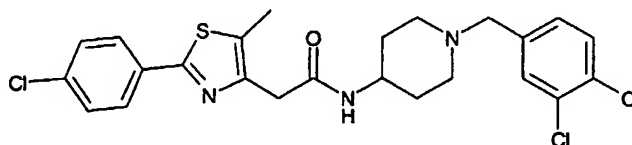
N-[1-(3,4-Dichlorobenzyl)-4-piperidinyl]-5-oxo-5-phenylpentanamide



The title compound was prepared from the product of 1-(3,4-dichlorobenzyl)-4-piperidinamine, di-trifluoroacetate salt (0.3g) and of 5-oxo-5-phenylpentanoic acid (0.134g) using the method of Example 94. Yield 0.149g as a solid MP: 130°C.

Example 97

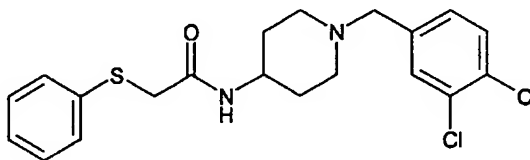
2-[2-(4-Chlorophenyl)-5-methyl-1,3-thiazol-4-yl]-N-[1-(3,4-dichlorobenzyl)-4-piperidinyl]acetamide



5 The title compound was prepared from the product of 1-(3,4-dichlorobenzyl)-4-piperidinamine, di-trifluoroacetate salt (0.3g) and 2-[2-(4-chlorophenyl)-5-methyl-1,3-thiazol-4-yl]acetic acid (0.187g) using the method of Example 94. Yield 0.1g as a solid MP: 170°C.

Example 98

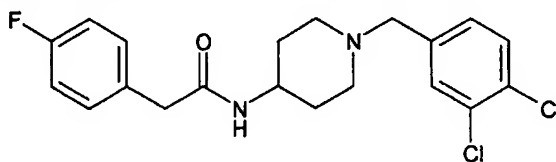
10 N-[1-(3,4-Dichlorobenzyl)-4-piperidinyl]-2-(phenylsulfanyl)acetamide



The title compound was prepared from the product of 1-(3,4-dichlorobenzyl)-4-piperidinamine, di-trifluoroacetate salt (0.3g) and 2-(phenylsulfanyl)acetic acid (0.118g) using the method of Example 94. Yield 0.056g as a solid MP: 97-99°C.

Example 99

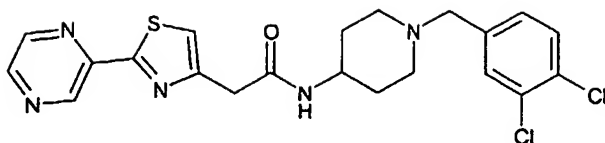
15 N-[1-(3,4-Dichlorobenzyl)-4-piperidinyl]-2-(4-fluorophenyl)acetamide



The title compound was prepared from the product of 1-(3,4-dichlorobenzyl)-4-piperidinamine, di-trifluoroacetate salt (0.3g) and 2-(4-fluorophenyl)acetic acid (0.108g) using the method of Example 94. Yield 0.15g as a solid MP: 144-7°C.

Example 100

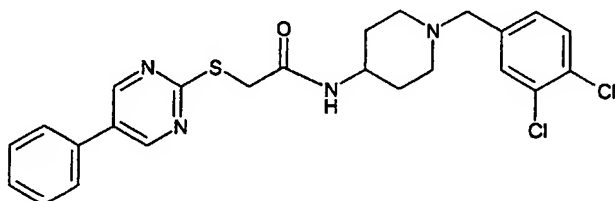
20 N-[1-(3,4-Dichlorobenzyl)-4-piperidinyl]-2-[2-(2-pyrazinyl)-1,3-thiazol-4-yl]acetamide



The title compound was prepared from the product of 1-(3,4-dichlorobenzyl)-4-piperidinamine, di-trifluoroacetate salt (0.3g) and 2-[2-(2-pyrazinyl)-1,3-thiazol-4-yl]acetic acid (0.155g) using the method of Example 94. Yield 0.08g as a solid MP: 186-9°C.

Example 101

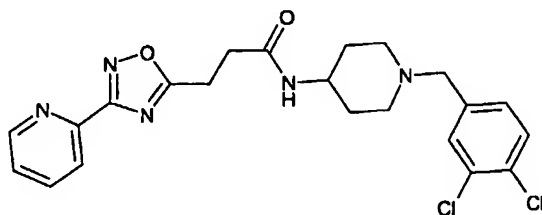
N-[1-(3,4-Dichlorobenzyl)-4-piperidinyl]-2-[(5-phenyl-2-pyrimidinyl)sulfanyl]acetamide



The title compound was prepared from the product of 1-(3,4-dichlorobenzyl)-4-piperidinamine, di-trifluoroacetate salt (0.3g) and 2-[(5-phenyl-2-pyrimidinyl)sulfanyl]acetic acid (0.172g) using the method of Example 94. Yield 0.115g as a solid MP: 157°C.

Example 102

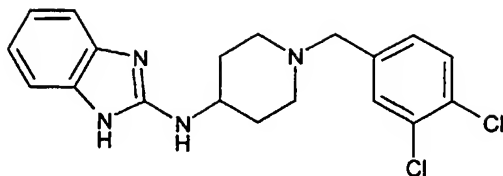
N-[1-(3,4-Dichlorobenzyl)-4-piperidinyl]-3-[3-(2-pyridinyl)-1,2,4-oxadiazol-5-yl]propanamide



The title compound was prepared from the product of 1-(3,4-dichlorobenzyl)-4-piperidinamine, di-trifluoroacetate salt (0.9g) and 3-[3-(2-pyridinyl)-1,2,4-oxadiazol-5-yl]propanoic acid (0.3g) using the method of Example 94. Yield 0.074g as a solid MP: 155°C.

Example 103

N-[1-(3,4-Dichlorobenzyl)-4-piperidinyl]-1H-benzimidazol-2-amine



(i) Ethyl 4-(1H-benzimidazol-2-ylamino)-1-piperidinecarboxylate

A solution of 2-chlorobenzimidazole (1g) and ethyl 4-amino-1-piperidinecarboxylate (2g) in 1-methyl-2-pyrrolidinone was heated at 130°C for 24h. The mixture was partitioned between water and ethyl acetate, the organic layer washed with water, dried and evaporated under reduced pressure. Purification was by chromatography eluting with 1% triethylamine/5% methanol in dichloromethane. Yield 0.630g as a solid.

(ii) N-(4-Piperidinyl)-1H-benzimidazol-2-amine, dihydrochloride salt

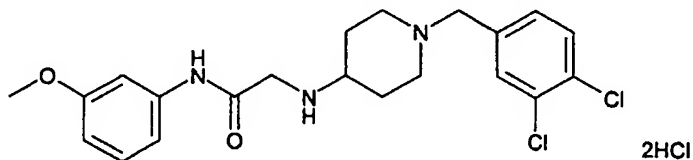
The product from step (i) (0.58g) was heated under reflux with 5M hydrochloric acid (20ml) for 24h. The solvent was evaporated under reduced pressure, the residue azeotroped with toluene, washed with ether. Yield 0.58g as a solid.

(iii) N-[1-(3,4-Dichlorobenzyl)-4-piperidinyl]-1H-benzimidazol-2-amine

Triethylamine (0.223ml) was added to a stirred suspension of the product from step (ii) (0.2g) in dimethylformamide. After 5min 3,4-dichlorobenzaldehyde (0.175g) then sodium triacetoxyborohydride (0.212g) was added and the mixture stirred at room temperature for 3h. The mixture was partitioned between 2M hydrochloric acid and ether, the aqueous layer was basified with aqueous sodium hydrogencarbonate and extracted with ethyl acetate. The organic layer was dried and evaporated under reduced pressure. The residue was triturated with ethyl acetate/ether and the solid collected. Yield 0.045g MP: 125°C.

Example 104

2-[[1-(3,4-Dichlorobenzyl)-4-piperidinyl]amino]-N-(3-methoxyphenyl)acetamide, dihydrochloride salt

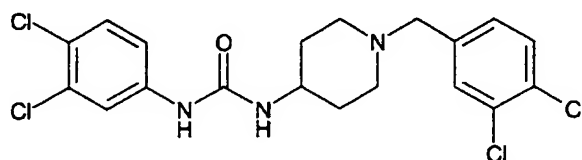


2-Chloro-N-(3-methoxyphenyl)-acetamide (0.241g) was added to a stirred solution of 1-(3,4-dichlorobenzyl)-4-piperidinamine, dihydrochloride salt (0.4g), triethylamine

(0.608g) in 1-methyl-2-pyrrolidinone (5ml). The reaction mixture was heated at 80°C for 6h then partitioned between ethyl acetate and brine. The organic layer was washed with brine, dried and evaporated under reduced pressure. Purification was by chromatography eluting with chloroform/isohexane/triethylamine/methanol 30:15:3:0.5. The resulting product was converted to the hydrochloride salt using ethereal hydrogenchloride. Yield 0.135g MP: 274-6°C.

Example 105

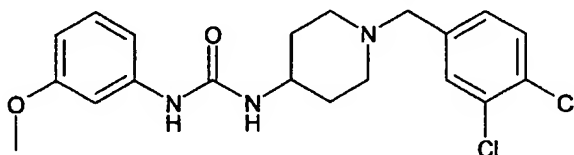
N-[1-(3,4-Dichlorobenzyl)-4-piperidinyl]-N'-(3,4-dichlorophenyl)urea



3,4-Dichlorophenyl isocyanate (0.081g) was added to a stirred solution of 1-(3,4-dichlorobenzyl)-4-piperidinamine, di-trifluoroacetate salt (0.13g), diisopropylethylamine (0.2g) in dichloromethane (4ml). The reaction mixture was stirred for 20h and the solvent removed under reduced pressure. Purification was by chromatography eluting with 5% methanol/dichloromethane. Yield 0.09g as a solid MP: 189-190°C.

Example 106

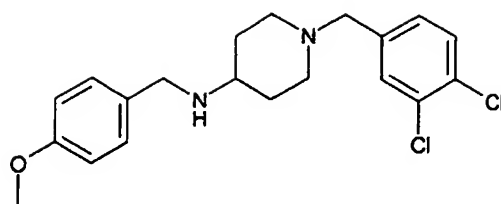
N-[1-(3,4-Dichlorobenzyl)-4-piperidinyl]-N'-(3-methoxyphenyl)urea



3-Methoxyphenyl isocyanate (0.064g) was added to a stirred solution of 1-(3,4-dichlorobenzyl)-4-piperidinamine, di-trifluoroacetate salt (0.13g), diisopropylethylamine (0.2g) in dichloromethane (4ml). The reaction mixture was stirred for 20h and the solvent removed under reduced pressure. Purification was by chromatography eluting with 5% methanol/dichloromethane. Yield 0.09g as a solid MP: 178-9°C.

Example 107

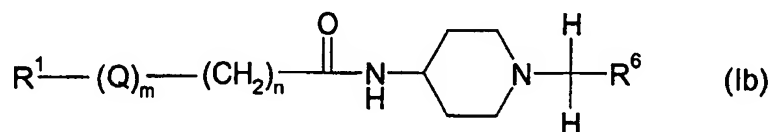
N-[1-(3,4-Dichlorobenzyl)-4-piperidinyl]-N-(4-methoxybenzyl)amine, dihydrochloride salt



2HCl

The title compound was prepared from 1-(3,4-dichlorobenzyl)-4-piperidinamine, di-trifluoroacetate salt (0.185g) and 4-methoxybenzaldehyde (0.49ul) using the method of Example A step (i). Yield 0.84g as a solid MP: >250°C.

5 The following table lists Examples 108-348 which are of compounds of formula (I) all of which accord to formula (Ib).



Example	R ¹	(Q) _m	n	R ⁶
108	phenyl	m=0	2	3,4-Cl ₂ -C ₆ H ₃
109	4-Br-C ₆ H ₄	m=0	1	3,4-Cl ₂ -C ₆ H ₃
110	4-NH ₂ -C ₆ H ₄	m=0	1	3,4-Cl ₂ -C ₆ H ₃
111	2-Br-C ₆ H ₄	m=0	1	3,4-Cl ₂ -C ₆ H ₃
112	4-F-C ₆ H ₄	m=0	1	3,4-Cl ₂ -C ₆ H ₃
113	3-CH ₃ -C ₆ H ₄	m=0	1	3,4-Cl ₂ -C ₆ H ₃
114	2-CH ₃ -C ₆ H ₄	m=0	1	3,4-Cl ₂ -C ₆ H ₃
115	3-Cl-4-OH-C ₆ H ₃	m=0	1	3,4-Cl ₂ -C ₆ H ₃
116	2-NO ₂ -C ₆ H ₄	m=0	1	3,4-Cl ₂ -C ₆ H ₃
117	2-Cl-C ₆ H ₄	m=0	1	3,4-Cl ₂ -C ₆ H ₃
118	4-Cl-C ₆ H ₄	m=0	1	3,4-Cl ₂ -C ₆ H ₃
119	3,4-(OH) ₂ -C ₆ H ₃	m=0	2	3,4-Cl ₂ -C ₆ H ₃
120	4-NO ₂ -C ₆ H ₄	m=0	1	3,4-Cl ₂ -C ₆ H ₃
121	phenyl	m=0	4	3,4-Cl ₂ -C ₆ H ₃
122	3,4-(OCH ₃) ₂ -C ₆ H ₃	m=0	1	3,4-Cl ₂ -C ₆ H ₃
123	3-F-4-OH-C ₆ H ₃	m=0	1	3,4-Cl ₂ -C ₆ H ₃
124	3,4-methylenedioxyphenyl	m=0	1	3,4-Cl ₂ -C ₆ H ₃

125	4-OH-C ₆ H ₄	m=0	2	3,4-Cl ₂ -C ₆ H ₃
126	4-OH-C ₆ H ₄	m=0	1	3,4-Cl ₂ -C ₆ H ₃
127	4-phenyl-phenyl	m=0	1	3,4-Cl ₂ -C ₆ H ₃
128	3,4-Cl ₂ -C ₆ H ₃	m=0	1	3,4-Cl ₂ -C ₆ H ₃
129	3-OH-C ₆ H ₄	m=0	2	3,4-Cl ₂ -C ₆ H ₃
130	4-CH ₃ -C ₆ H ₄	m=0	2	3,4-Cl ₂ -C ₆ H ₃
131	4-NO ₂ -C ₆ H ₄	m=0	3	3,4-Cl ₂ -C ₆ H ₃
132	3,4-(OCH ₃) ₂ -C ₆ H ₃	m=0	2	3,4-Cl ₂ -C ₆ H ₃
133	C ₆ F ₅	m=0	2	3,4-Cl ₂ -C ₆ H ₃
134	4-CH ₃ -C ₆ H ₄	m=0	1	3,4-Cl ₂ -C ₆ H ₃
135	4-OCF ₃ -C ₆ H ₄	m=0	1	3,4-Cl ₂ -C ₆ H ₃
136	3,4-(OCH ₃) ₂ -C ₆ H ₃	m=0	3	3,4-Cl ₂ -C ₆ H ₃
137	4-OCH ₃ -C ₆ H ₄	m=0	1	3,4-Cl ₂ -C ₆ H ₃
138	4-N(CH ₃) ₂ -C ₆ H ₄	m=0	1	3,4-Cl ₂ -C ₆ H ₃
139	4-OCH ₃ -C ₆ H ₄	m=0	2	3,4-Cl ₂ -C ₆ H ₃
140	3,4,5-(OCH ₃) ₃ -C ₆ H ₂	m=0	1	3,4-Cl ₂ -C ₆ H ₃
141	3,4-methylenedioxyphenyl	m=0	2	3,4-Cl ₂ -C ₆ H ₃
142	3-NH ₂ -C ₆ H ₄	m=0	1	3,4-Cl ₂ -C ₆ H ₃
143	naphth-1-yl	m=0	1	3,4-Cl ₂ -C ₆ H ₃
144	3-OCH ₃ -4-OH-C ₆ H ₃	m=0	1	3,4-Cl ₂ -C ₆ H ₃
145	3-(6-Br-1-(prop-2-en-1-yl)-naphth-2-yloxymethyl)phenyl	m=0	1	3,4-Cl ₂ -C ₆ H ₃
146	4-(4-NO ₂ -C ₆ H ₄ -CH ₂ O)-C ₆ H ₄	m=0	1	3,4-Cl ₂ -C ₆ H ₃
147	3-F-4-CH ₃ O-C ₆ H ₃	m=0	1	3,4-Cl ₂ -C ₆ H ₃
148	3-CH ₃ -C ₆ H ₄	m=0	4	3,4-Cl ₂ -C ₆ H ₃
149	3-OH-C ₆ H ₄	m=0	1	3,4-Cl ₂ -C ₆ H ₃
150	4-(C ₆ H ₅ -CH ₂ O)-C ₆ H ₄	m=0	1	3,4-Cl ₂ -C ₆ H ₃
151	4-(3-NO ₂ -C ₆ H ₄)-C ₆ H ₄	m=0	1	3,4-Cl ₂ -C ₆ H ₃
152	2,5-(CH ₃) ₂ -C ₆ H ₃	m=0	1	3,4-Cl ₂ -C ₆ H ₃

153	4-I-C ₆ H ₄	m=0	1	3,4-Cl ₂ -C ₆ H ₃
154	3-Br-C ₆ H ₄	m=0	1	3,4-Cl ₂ -C ₆ H ₃
155	2-CH ₃ -3-NO ₂ -C ₆ H ₃	m=0	1	3,4-Cl ₂ -C ₆ H ₃
156	3-OH-4-OCH ₃ -C ₆ H ₃	m=0	1	3,4-Cl ₂ -C ₆ H ₃
157	3-F-C ₆ H ₄	m=0	1	3,4-Cl ₂ -C ₆ H ₃
158	2-F-C ₆ H ₄	m=0	1	3,4-Cl ₂ -C ₆ H ₃
159	3,5-(OCH ₃) ₂ -C ₆ H ₃	m=0	1	3,4-Cl ₂ -C ₆ H ₃
160	3-Cl-C ₆ H ₄	m=0	1	3,4-Cl ₂ -C ₆ H ₃
161	phenyl	m=0	1	3,4-Cl ₂ -C ₆ H ₃
162	3,5-(CH ₃) ₂ -C ₆ H ₃	m=0	1	3,4-Cl ₂ -C ₆ H ₃
163	3-OCH ₃ -C ₆ H ₄	m=0	2	3,4-Cl ₂ -C ₆ H ₃
164	2,4-F ₂ -C ₆ H ₃	m=0	1	3,4-Cl ₂ -C ₆ H ₃
165	2-OCH ₃ -C ₆ H ₄	m=0	1	3,4-Cl ₂ -C ₆ H ₃
166	3,4-F ₂ -C ₆ H ₃	m=0	1	3,4-Cl ₂ -C ₆ H ₃
167	3,5-F ₂ -C ₆ H ₃	m=0	1	3,4-Cl ₂ -C ₆ H ₃
168	Pyridin-3-yl	m=0	1	3,4-Cl ₂ -C ₆ H ₃
169	Pyridin-2-yl	m=0	1	3,4-Cl ₂ -C ₆ H ₃
170	5-Br-pyridin-3-yl	m=0	1	3,4-Cl ₂ -C ₆ H ₃
171	2,4-(OCH ₃) ₂ -C ₆ H ₃	m=0	1	3,4-Cl ₂ -C ₆ H ₃
172	4-(benzyloxy)phenyl	m=0	1	3,4-Cl ₂ -C ₆ H ₃
173	3-(benzyloxy)phenyl	m=0	1	3,4-Cl ₂ -C ₆ H ₃
174	2-methyl-naphth-1-yl	m=0	1	3,4-Cl ₂ -C ₆ H ₃
175	2-CH ₃ CH ₂ O-C ₆ H ₄	m=0	1	3,4-Cl ₂ -C ₆ H ₃
176	3,4-(OCH ₃) ₂ -C ₆ H ₃	m=0	1	3,4-Cl ₂ -C ₆ H ₃
177	4-CH ₃ (CH ₂) ₃ O-C ₆ H ₄	m=0	1	3,4-Cl ₂ -C ₆ H ₃
178	Indol-1-yl	m=0	1	3,4-Cl ₂ -C ₆ H ₃
179	2-NO ₂ -C ₆ H ₄	m=0	1	3,4-Cl ₂ -C ₆ H ₃
180	Thien-2-yl	m=0	1	3,4-Cl ₂ -C ₆ H ₃
181	3-Cl-4-OH-C ₆ H ₃	m=0	1	3,4-Cl ₂ -C ₆ H ₃
182	2,4-Cl ₂ -C ₆ H ₃	m=0	1	3,4-Cl ₂ -C ₆ H ₃
183	2,6-Cl ₂ -C ₆ H ₃	m=0	1	3,4-Cl ₂ -C ₆ H ₃

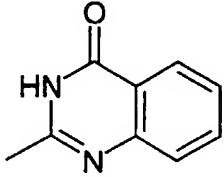
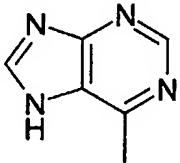
184	2-Br-C ₆ H ₄	m=0	1	3,4-Cl ₂ -C ₆ H ₃
185	3,4-Cl ₂ -C ₆ H ₃	m=0	1	3,4-Cl ₂ -C ₆ H ₃
186	3-Br-C ₆ H ₄	m=0	1	3,4-Cl ₂ -C ₆ H ₃
187	3,5-F ₂ -C ₆ H ₃	m=0	1	3,4-Cl ₂ -C ₆ H ₃
188	3-NH ₂ -C ₆ H ₄	m=0	1	3,4-Cl ₂ -C ₆ H ₃
189	2-(ClCH ₂ C(O)NH)- thiazol-4-yl	m=0	1	3,4-Cl ₂ -C ₆ H ₃
190	3-Cl-C ₆ H ₄	m=0	1	3,4-Cl ₂ -C ₆ H ₃
191	2,5-(OCH ₃) ₂ -C ₆ H ₃	m=0	1	3,4-Cl ₂ -C ₆ H ₃
192	4-OH-C ₆ H ₄	m=0	1	3,4-Cl ₂ -C ₆ H ₃
193	Indol-3-yl	m=0	1	3,4-Cl ₂ -C ₆ H ₃
194	5-OCH ₃ -indol-3-yl	m=0	1	3,4-Cl ₂ -C ₆ H ₃
195	Naphth-2-yl	m=0	1	3,4-Cl ₂ -C ₆ H ₃
196	4-CH ₃ -C ₆ H ₄	m=0	1	3,4-Cl ₂ -C ₆ H ₃
197	3,4,5-(OCH ₃) ₃ -C ₆ H ₂	m=0	1	3,4-Cl ₂ -C ₆ H ₃
198	4-CH ₃ (CH ₂) ₃ O-C ₆ H ₄	m=0	1	3,4-Cl ₂ -C ₆ H ₃
199	4-S(O) ₂ CH ₃ -C ₆ H ₄	m=0	1	3,4-Cl ₂ -C ₆ H ₃
200	2,4,6-(CH ₃) ₃ -C ₆ H ₂	m=0	1	3,4-Cl ₂ -C ₆ H ₃
201	4-F-C ₆ H ₄	m=0	1	3,4-Cl ₂ -C ₆ H ₃
202	2-(pyrazin-2-yl)-thiazol-4- yl	m=0	1	3,4-Cl ₂ -C ₆ H ₃
203	2-CH ₃ -5-(CH ₃) ₂ CH-indol- 3-yl	m=0	1	3,4-Cl ₂ -C ₆ H ₃
204	5-(pyrrolidin-1-yl)- tetrazol-2-yl	m=0	1	3,4-Cl ₂ -C ₆ H ₃
205	5-(4-CH ₃ -phenyl)-tetrazol- 2-yl	m=0	1	3,4-Cl ₂ -C ₆ H ₃
206	3,5-F ₂ -C ₆ H ₃	m=0	1	3,4-Cl ₂ -C ₆ H ₃
207	3-OCH ₃ -C ₆ H ₄	m=0	1	3,4-Cl ₂ -C ₆ H ₃
208	5-Cl-benzo[b]thiophen-3- yl	m=0	1	3,4-Cl ₂ -C ₆ H ₃

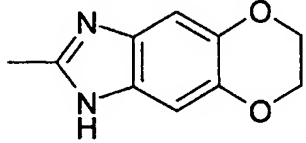
209	3,4-Cl ₂ -C ₆ H ₃	m=0	1	3,4-Cl ₂ -C ₆ H ₃
210	2-phenyl-5-methyl-thiazol-4-yl	m=0	1	3,4-Cl ₂ -C ₆ H ₃
211	4-OCF ₃ -C ₆ H ₄	m=0	1	3,4-Cl ₂ -C ₆ H ₃
212	3-methyl-5-Cl-benzo[b]thiophen-2-yl	m=0	1	3,4-Cl ₂ -C ₆ H ₃
213	3-methyl-benzo[b]thiophen-2-yl	m=0	1	3,4-Cl ₂ -C ₆ H ₃
214	2-NO ₂ -C ₆ H ₄	m=0	1	3,4-Cl ₂ -C ₆ H ₃
215	3-NO ₂ -1,2,4-triazol-1-yl	m=0	1	3,4-Cl ₂ -C ₆ H ₃
216	3,4-(NO ₂) ₂ -5-CH ₃ -pyrazol-1-yl	m=0	1	3,4-Cl ₂ -C ₆ H ₃
217	4-(CH ₃) ₂ CH(CH ₂) ₂ O-C ₆ H ₄	m=0	1	3,4-Cl ₂ -C ₆ H ₃
218	2,3-(CH ₃) ₂ -indol-5-yl	m=0	1	3,4-Cl ₂ -C ₆ H ₃
219	3,5-(CH ₃) ₂ -4-Cl-pyrazol-1-yl	m=0	1	3,4-Cl ₂ -C ₆ H ₃
220	3,5-(CH ₃) ₂ -4-NO ₂ -pyrazol-1-yl	m=0	1	3,4-Cl ₂ -C ₆ H ₃
221	2,4-(NO ₂) ₂ -imidazol-1-yl	m=0	1	3,4-Cl ₂ -C ₆ H ₃
222	4-NO ₂ -imidazol-1-yl	m=0	1	3,4-Cl ₂ -C ₆ H ₃
223	3,5-(CH ₃) ₂ -pyrazol-1-yl	m=0	1	3,4-Cl ₂ -C ₆ H ₃
224	4-CH ₃ (CH ₂) ₅ -C ₆ H ₄	m=0	1	3,4-Cl ₂ -C ₆ H ₃
225	2-CN-C ₆ H ₄	m=0	1	3,4-Cl ₂ -C ₆ H ₃
226	4-Cl-C ₆ H ₄	O	1	4-Cl-C ₆ H ₄
227	4-Cl-C ₆ H ₄	O	1	2-Br-C ₆ H ₄
228	4-Cl-C ₆ H ₄	O	1	3-(CO ₂ CH ₃)-4-Br-C ₆ H ₄
229	4-Cl-C ₆ H ₄	O	1	4-NO ₂ -C ₆ H ₄
230	4-Cl-C ₆ H ₄	O	1	3-benzoyl-phenyl
231	4-Cl-C ₆ H ₄	O	1	5-OCH ₃ -benzimidazol-2-yl

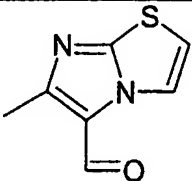
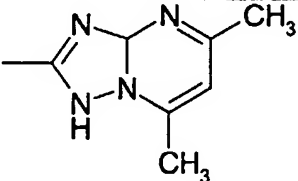
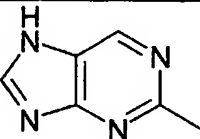
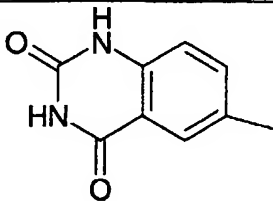
232	4-Cl-C ₆ H ₄	O	1	4-Br-C ₆ H ₄
233	4-Cl-C ₆ H ₄	O	1	4-(1,2,3-thiadiazol-4-yl)-phenyl
234	4-Cl-C ₆ H ₄	O	1	4-CH ₃ -C ₆ H ₄
235	4-Cl-C ₆ H ₄	O	1	4-(2,6-Cl ₂ -C ₆ H ₃)CH ₂ S(O) ₂ -C ₆ H ₄
236	4-Cl-C ₆ H ₄	O	1	3,5-Br ₂ -C ₆ H ₃
237	4-Cl-C ₆ H ₄	O	1	Indan-5-yl
238	4-Cl-C ₆ H ₄	O	1	2-F-3-Cl-C ₆ H ₃
239	4-Cl-C ₆ H ₄	O	1	benzofurazan-5-yl
240	4-Cl-C ₆ H ₄	O	1	7-Cl-quinolin-2-yl
241	4-F-C ₆ H ₄	m=0	1	2,5-Cl ₂ -C ₆ H ₃
242	4-F-C ₆ H ₄	m=0	1	2,3-Cl ₂ -C ₆ H ₃
243	4-F-C ₆ H ₄	m=0	1	4-F-C ₆ H ₄
244	4-F-C ₆ H ₄	m=0	1	3-CO ₂ CH ₃ -4-Br-C ₆ H ₃
245	4-F-C ₆ H ₄	m=0	1	4-NO ₂ -C ₆ H ₄
246	4-F-C ₆ H ₄	m=0	1	3-benzoyl-phenyl
247	4-F-C ₆ H ₄	m=0	1	4-CH ₃ -naphth-1-yl
248	4-F-C ₆ H ₄	m=0	1	3,4-methylene-dioxyphenyl
249	4-F-C ₆ H ₄	m=0	1	5-OCH ₃ -benzimidazol-2-yl
250	4-F-C ₆ H ₄	m=0	1	3-NO ₂ -4-CH ₃ -C ₆ H ₃
251	4-F-C ₆ H ₄	m=0	1	3,4-(CH ₃) ₂ -C ₆ H ₃
252	4-F-C ₆ H ₄	m=0	1	3-CH ₃ -4-OCH ₃ -C ₆ H ₃
253	4-F-C ₆ H ₄	m=0	1	4-(2-C(O)NH ₂ -C ₆ H ₄)-C ₆ H ₄

254	4-F-C ₆ H ₄	m=0	1	4-Br-C ₆ H ₄
255	4-F-C ₆ H ₄	m=0	1	4-(2,6-Cl ₂ -C ₆ H ₄)CH ₂ S(O) ₂ -C ₆ H ₄
256	3-(pyridin-2-yl)-1,2,4-oxadiazol-5-yl	m=0	2	4-Cl-C ₆ H ₄
257	3-(pyridin-2-yl)-1,2,4-oxadiazol-5-yl	m=0	2	3-Cl-4-OCH ₃ -C ₆ H ₃
258	3-(pyridin-2-yl)-1,2,4-oxadiazol-5-yl	m=0	2	2,3-Cl ₂ -C ₆ H ₃
259	3-(pyridin-2-yl)-1,2,4-oxadiazol-5-yl	m=0	2	4-F-C ₆ H ₄
260	3-(pyridin-2-yl)-1,2,4-oxadiazol-5-yl	m=0	2	3-CF ₃ -C ₆ H ₄
261	3-(pyridin-2-yl)-1,2,4-oxadiazol-5-yl	m=0	2	4-NO ₂ -C ₆ H ₄
262	3-(pyridin-2-yl)-1,2,4-oxadiazol-5-yl	m=0	2	3-benzoyl-phenyl
263	3-(pyridin-2-yl)-1,2,4-oxadiazol-5-yl	m=0	2	3,4-methylene-dioxyphenyl
264	3-(pyridin-2-yl)-1,2,4-oxadiazol-5-yl	m=0	2	3,5-(CH ₃) ₂ -C ₆ H ₃
265	3-(pyridin-2-yl)-1,2,4-oxadiazol-5-yl	m=0	2	3-NO ₂ -4-CH ₃ -C ₆ H ₃
266	3-(pyridin-2-yl)-1,2,4-oxadiazol-5-yl	m=0	2	3,4-(CH ₃) ₂ -C ₆ H ₃
267	3-(pyridin-2-yl)-1,2,4-oxadiazol-5-yl	m=0	2	3-CH ₃ -C ₆ H ₄
268	3-(pyridin-2-yl)-1,2,4-oxadiazol-5-yl	m=0	2	3-CH ₃ -4-OCH ₃ -C ₆ H ₄

269	3-(pyridin-2-yl)-1,2,4-oxadiazol-5-yl	m=0	2	4-Br-C ₆ H ₄
270	3-(pyridin-2-yl)-1,2,4-oxadiazol-5-yl	m=0	2	Indan-5-yl
271	3-(pyridin-2-yl)-1,2,4-oxadiazol-5-yl	m=0	2	4-CF ₃ -C ₆ H ₄
272	3-(pyridin-2-yl)-1,2,4-oxadiazol-5-yl	m=0	2	Naphth-2-yl
273	3-(pyridin-2-yl)-1,2,4-oxadiazol-5-yl	m=0	2	4-CH ₃ -C ₆ H ₄
274	3-(pyridin-2-yl)-1,2,4-oxadiazol-5-yl	m=0	2	benzofurazan-5-yl
275	3-(pyridin-2-yl)-1,2,4-oxadiazol-5-yl	m=0	2	3,4-F ₂ -C ₆ H ₃
276	3-(pyridin-2-yl)-1,2,4-oxadiazol-5-yl	m=0	2	7-Cl-quinolin-2-yl
277	3-(pyridin-2-yl)-1,2,4-oxadiazol-5-yl	m=0	2	3-Cl-C ₆ H ₄
278	3-(pyridin-2-yl)-1,2,4-oxadiazol-5-yl	m=0	2	4-CF ₃ -C ₆ H ₄
279	3-(pyridin-2-yl)-1,2,4-oxadiazol-5-yl	m=0	2	4-CH ₃ -C ₆ H ₄
280	4-OCH ₃ -C ₆ H ₄	O	1	3,4-Cl ₂ -C ₆ H ₃
281	4-Cl-C ₆ H ₄	O	1	3,4-Cl ₂ -C ₆ H ₃
282	4-NO ₂ -C ₆ H ₄	O	1	3,4-Cl ₂ -C ₆ H ₃
283	4-NHC(O)CH ₃ -C ₆ H ₄	O	1	3,4-Cl ₂ -C ₆ H ₃
284	4-O(CH ₂) ₂ CH ₃ -C ₆ H ₄	O	1	3,4-Cl ₂ -C ₆ H ₃
285	3-CO ₂ CH ₂ CH ₃ -C ₆ H ₄	O	1	3,4-Cl ₂ -C ₆ H ₃
286	2-C(CH ₃) ₃ -C ₆ H ₄	O	1	3,4-Cl ₂ -C ₆ H ₃
287	2-NHC(O)CH ₃ -C ₆ H ₄	O	1	3,4-Cl ₂ -C ₆ H ₃

288	3,5-(OCH ₃) ₂ -C ₆ H ₃	O	1	3,4-Cl ₂ -C ₆ H ₃
289	2-OCH ₃ -5-NO ₂ -C ₆ H ₃	O	1	3,4-Cl ₂ -C ₆ H ₃
290	4-CN-C ₆ H ₄	O	1	3,4-Cl ₂ -C ₆ H ₃
291	2-Cl-5-CF ₃ -C ₆ H ₃	O	1	3,4-Cl ₂ -C ₆ H ₃
292	2-NO ₂ -5-CH ₃ -C ₆ H ₃	O	1	3,4-Cl ₂ -C ₆ H ₃
293	3-Cl-5-OCH ₃ -C ₆ H ₃	O	1	3,4-Cl ₂ -C ₆ H ₃
294	3-NO ₂ -C ₆ H ₄	O	1	3,4-Cl ₂ -C ₆ H ₃
295	3-Br-C ₆ H ₄	O	1	3,4-Cl ₂ -C ₆ H ₃
296	4-I-C ₆ H ₄	O	1	3,4-Cl ₂ -C ₆ H ₃
297	3,5-F ₂ -C ₆ H ₃	O	1	3,4-Cl ₂ -C ₆ H ₃
298	4,6-(NH ₂) ₂ -pyrimidin-2-yl	S	1	3,4-F ₂ -C ₆ H ₃
299	Benzimidazol-2-yl	S	1	3,4-F ₂ -C ₆ H ₃
300	Thiazol-2-yl	S	1	3,4-F ₂ -C ₆ H ₃
301		S	1	3,4-F ₂ -C ₆ H ₃
302	5-NO ₂ -benzimidazol-2-yl	S	1	3,4-F ₂ -C ₆ H ₃
303	Pyridin-2-yl	S	1	3,4-F ₂ -C ₆ H ₃
304		S	1	3,4-F ₂ -C ₆ H ₃
305	1H-1,2,4-triazol-3-yl	S	1	3,4-F ₂ -C ₆ H ₃
306	Pyrimidin-2-yl	S	1	3,4-F ₂ -C ₆ H ₃
307	1-phenyl-tetrazol-5-yl	S	1	3,4-F ₂ -C ₆ H ₃
308	4,6-(CH ₃) ₂ -pyrimidin-2-yl	S	1	3,4-F ₂ -C ₆ H ₃
309	4-(thiophen-2-yl)- pyrimidin-2-yl	S	1	3,4-F ₂ -C ₆ H ₃
310	2-(cyclopropyl-CH ₂ S)- 1,3,4-thiadiazol-5-yl	S	1	3,4-F ₂ -C ₆ H ₃

311	4-methyl-3-(thiophen-2-yl)-1,2,4-triazol-5-yl	S	1	3,4-F ₂ -C ₆ H ₃
312	3-CN-6-(CH ₃ C(O))-pyridin-2-yl	S	1	3,4-F ₂ -C ₆ H ₃
313	1H-pyrazolo[3,4-d]pyrimidin-4-yl	S	1	3,4-F ₂ -C ₆ H ₃
314	5-OCH ₃ -benzimidazol-2-yl	S	1	3,4-F ₂ -C ₆ H ₃
315	5-F-6-Cl-benzimidazol-2-yl	S	1	3,4-F ₂ -C ₆ H ₃
316	4,5-dihydrothiazol-2-yl	S	1	3,4-F ₂ -C ₆ H ₃
317	1H-5-phenyl-1,2,4-triazol-3-yl	S	1	3,4-F ₂ -C ₆ H ₃
318	2-(thiophen-2-yl)-1,3,4-oxadiazol-5-yl	S	1	3,4-F ₂ -C ₆ H ₃
319	Quinoxalin-2-yl	S	1	3,4-F ₂ -C ₆ H ₃
320	2,5-Cl ₂ -C ₆ H ₃	S	1	3,4-F ₂ -C ₆ H ₃
321	2-(pyridin-2-yl)-1,3,4-oxadiazol-5-yl	S	1	3,4-F ₂ -C ₆ H ₃
322	7-CF ₃ -quinolin-4-yl	S	1	3,4-F ₂ -C ₆ H ₃
323	2-(pyridin-2-yl)-4-CH ₃ -pyrimidin-6-yl	S	1	3,4-F ₂ -C ₆ H ₃
324	Naphth-1-yl	S	1	3,4-F ₂ -C ₆ H ₃
325	3,4-(OCH ₃) ₂ -C ₆ H ₃	S	1	3,4-F ₂ -C ₆ H ₃
326	1,3,4-thiadiazol-2-yl	S	1	3,4-F ₂ -C ₆ H ₃
327	3-CF ₃ -C ₆ H ₄	S	1	3,4-F ₂ -C ₆ H ₃
328		S	1	3,4-F ₂ -C ₆ H ₃
329	3,4-Cl ₂ -C ₆ H ₃	S	1	3,4-F ₂ -C ₆ H ₃
330	3-CN-5-CH ₃ -pyridin-2-yl	S	1	3,4-F ₂ -C ₆ H ₃

331	4-phenyl-thiazol-2-yl	S	1	3,4-F ₂ -C ₆ H ₃
332		S	1	3,4-F ₂ -C ₆ H ₃
333	2-CH ₃ -1,3,4-thiadiazol-5-yl	S	1	3,4-F ₂ -C ₆ H ₃
334		S	1	3,4-F ₂ -C ₆ H ₃
335		S	1	3,4-F ₂ -C ₆ H ₃
336	2-phenoxy-phenyl	S	1	3,4-F ₂ -C ₆ H ₃
337	2-OCH ₃ -C ₆ H ₄	S	1	3,4-F ₂ -C ₆ H ₃
338	2-CH ₃ -4-Cl-C ₆ H ₃	S	1	3,4-F ₂ -C ₆ H ₃
339	2-CH ₃ -6-Cl-C ₆ H ₃	S	1	3,4-F ₂ -C ₆ H ₃
340	2-(HC≡C-CH ₂ S)-1,3,4-thiadiazol-5-yl	S	1	3,4-F ₂ -C ₆ H ₃
341	2-CO ₂ CH ₃ -C ₆ H ₄	S	1	3,4-F ₂ -C ₆ H ₃
342	4-CN-C ₆ H ₄	O	1	3,4-F ₂ -C ₆ H ₃
343	4-((CH ₃) ₂ NCH ₂)-C ₆ H ₄	O	1	3,4-F ₂ -C ₆ H ₃
344		O	1	3,4-F ₂ -C ₆ H ₃
345	3-CH ₂ OH-C ₆ H ₄	O	1	3,4-F ₂ -C ₆ H ₃
346	2-OCH ₂ CH ₂ OH-C ₆ H ₄	O	1	3,4-F ₂ -C ₆ H ₃
347	4-CH ₃ (CH ₂) ₂ O-C ₆ H ₄	O	1	3,4-F ₂ -C ₆ H ₃

348	3-Cl-5-OCH ₃ -C ₆ H ₃	O	1	3,4-F ₂ -C ₆ H ₃
-----	--	---	---	---

General Preparation of Examples 108-225

PyBroP® (bromo-tris-pyrrolidino-phosphonium hexafluorophosphate, 2 equivalents) was added to a solution of 1-(3,4-dichlorobenzyl)-4-piperidinamine, hydrochloride salt (1mg) the appropriate acid (2 equivalents) and triethylamine in 1-methyl-2-pyrrolidone (0.2ml) and was left for 24h. The reaction mixture was evaporated to dryness and the residue was dissolved in dimethylsulfoxide (0.3ml).

General Preparation of Examples 225-240

Step i: *tert*-Butyl 4-[[{(4-chlorophenoxy)acetyl]amino}-1-piperidinecarboxylate

Prepared following the method of Example 94 using (4-chlorophenoxy)acetic acid (0.50g), 1,1-carbonyldiimidazole (0.50g) and *tert*-butyl 4-amino-1-piperidinecarboxylate (0.46g) to give the subtitle compound (0.54g).

Step ii: 2-(4-chlorophenoxy)-*N*-(4-piperidinyl)acetamide

Prepared following the method of Example A step (ii) using *tert*-butyl 4-[[{(4-chlorophenoxy)acetyl]amino}-1-piperidinecarboxylate (0.52g) to give the subtitle compound (0.35g).

Step iii: Final product

A mixture of the product from step (ii) (1.07mg), the appropriate alkyl halide (2 equivalents) and *N,N*-diisopropylethylamine (3 equivalents) in 1-methyl-2-pyrrolidinone (0.18ml) was left at room temperature for 24h. The mixture was evaporated to dryness and the residue was dissolved in dimethylsulfoxide (0.4ml).

General Preparation of Examples 241-255

A mixture of 2-(4-fluorophenyl)-*N*-(4-piperidinyl)acetamide (WO97/36871; 0.94mg), the appropriate alkyl halide (2 equivalents) and *N,N*-diisopropylethylamine (3 equivalents) in 1-methyl-2-pyrrolidinone (0.18ml) was left at room temperature for 24h. The mixture was evaporated to dryness and the residue was dissolved in dimethylsulfoxide (0.4ml).

General Preparation of Examples 256-279

Step i: *tert*-Butyl 4-({3-[3-(2-pyridinyl)-1,2,4-oxadiazol-5-yl]propanoyl}amino)-1-piperidinecarboxylate

3-[3-(2-Pyridinyl)-1,2,4-oxadiazol-5-yl]propanoic acid (0.60g) was dissolved in dichloromethane (10ml). 1,1-Carbonyldiimidazole (0.33g) was added followed by *tert*-butyl 4-amino-1-piperidinecarboxylate hydrochloride (0.5g) and triethylamine (0.31ml). After 2 hours water, brine and dichloromethane were added and the phases separated. The organic phase was dried, filtered and evaporated and the residue was purified by chromatography eluting with ethyl acetate : methanol (33:1) to give the subtitle compound (0.40g).

Step ii: *N*-(4-Piperidinyl)-3-[3-(2-pyridinyl)-1,2,4-oxadiazol-5-yl]propanamide

tert-Butyl 4-({3-[3-(2-pyridinyl)-1,2,4-oxadiazol-5-yl]propanoyl}amino)-1-piperidinecarboxylate (0.40g) was dissolved in dichloromethane (6ml) and trifluoroacetic acid (3ml) was added. After 2 hours water, 2N sodium hydroxide and dichloromethane were added and the phases were separated. The organic phase was dried, filtered and evaporated to give the subtitle compound (0.19g).

Step iii: Final product

A mixture of the product from step (ii) (1.21mg), the appropriate alkyl halide (2 equivalents) and *N,N*-diisopropylethylamine (3 equivalents) in 1-methyl-2-pyrrolidinone (0.18ml) was left at room temperature for 24h. The mixture was evaporated to dryness and the residue was dissolved in dimethylsulfoxide (0.4ml).

General Preparation of Examples 280-296

Step i: 2-Chloro-*N*-[1-(3,4-dichlorobenzyl)-4-piperidinyl]acetamide

Prepared following the general preparation method of Examples 297-357 step (iii) using 1-(3,4-dichlorobenzyl)-4-piperidinamine hydrochloride (2.0g), *N,N*-diisopropylethylamine (5.55 ml) and chloroacetyl chloride (0.55ml) to give the subtitle compound (1.0g).

Step ii: Final Product

A mixture of the product from step (i) (1.34 mg), the appropriate phenol (1.5 equivalents) and potassium *tert*-butoxide (1.4 equivalents) in 1-methyl-2-pyrrolidinone (0.13ml) was left at room temperature for 24 hours. The mixture was evaporated to dryness and the residue was dissolved in dimethylsulfoxide (0.4ml).

General Preparation of Examples 297-340

Step i: Carbamic acid, [1-[(3,4-difluorophenyl)methyl]-4-piperidinyl]-, 1,1-dimethylethyl ester

Carbamic acid, 4-piperidinyl-, 1,1-dimethylethyl ester (6.95g) was dissolved in *N,N*-dimethylformamide (70ml). 3,4-Difluorobenzylbromide (4.55ml) and potassium carbonate (16.0g) were added. The mixture was heated to reflux for 16hours, then allowed to cool to room temperature. Ammonium chloride solution was added and the mixture was extracted thrice with ethyl acetate. The organic phases were washed with water (twice) and brine, then dried, filtered and evaporated. The residue was triturated with ether : *iso*-hexane (1:1) to give the subtitle compound (8.13g)

Step ii: 1-[(3,4-Difluorophenyl)methyl]-piperidin-4-ylamine dihydrochloride

Carbamic acid, [1-[(3,4-difluorophenyl)methyl]-4-piperidinyl]-, 1,1-dimethylethyl ester was suspended in 6N hydrochloric acid (100ml). After 16hours excess hydrochloric acid was evaporated and the residue azeotroped with toluene, dried and evaporated to give the subtitle compound (8.10g).

Step iii: 2-Chloro-*N*-[1-[(3,4-difluorophenyl)methyl]-piperidin-4-yl]-acetamide

1-[(3,4-Difluorophenyl)methyl]-piperidin-4-ylamine dihydrochloride (3.18g) was dissolved in tetrahydrofuran (40ml). Diisopropylethylamine (6.84g) and chloroacetyl chloride (1.33g) were added. After 3hours water, brine and ethyl acetate were added the phase were separated. The organic phase was dried, filtered and evaporated and the residue was purified by chromatography eluting with ethyl acetate to give the subtitle compound (0.728g).

Step iv: Final Product

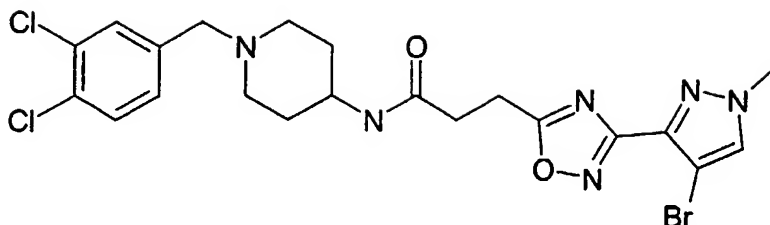
The product from step (iii) (1.21mg) was dissolved in dimethylsulfoxide (50μl) and diisopropylethylamine (1.55mg, 3 equivalents) was added as a solution in dimethylsulfoxide (50μl). The appropriate thiol was added (1 equivalent) in dimethylsulfoxide (40μl) and the reaction mixture was left at room temperature for 24hours. The reaction mixture was evaporated to dryness and the residue was dissolved in dimethylsulfoxide (400μl).

General Preparation of Examples 341-348

Prepared from the product of general preparation for Examples 297-340 step (iii) and the appropriate phenol following the method of Examples 280-296 step (ii).

Example 351

3-[3-(4-Bromo-1-methyl-1*H*-pyrazol-3-yl)-1,2,4-oxadiazol-5-yl]-*N*-[1-(3,4-dichlorobenzyl)-4-piperidinyl]propanamide



Step i: Methyl 4-{[1-(3,4-dichlorobenzyl)-4-piperidinyl]amino}-4-oxobutanoate

To a solution of 1-(3,4-dichlorobenzyl)-4-piperidinamine hydrochloride (3.50g) in dichloromethane (100ml) was added methyl 4-chloro-4-oxobutanoate (2.00g) dropwise.

5 Triethylamine (3.90g) was added and the reaction stirred under nitrogen for 2 hours.

Saturated sodium hydrogen carbonate solution was then added, with the solution being extracted three times with dichloromethane. The pooled organic phase was washed once with water, once with saturated brine and dried over anhydrous magnesium sulfate. After filtration the solvent was removed under reduced pressure to leave methyl 4-{[1-(3,4-dichlorobenzyl)-4-piperidinyl]amino}-4-oxobutanoate (3.00g).

10

Step ii: Lithium 4-{[1-(3,4-dichlorobenzyl)-4-piperidinyl]amino}-4-oxobutanoate

To a solution of methyl 4-{[1-(3,4-dichlorobenzyl)-4-piperidinyl]amino}-4-oxobutanoate (3.72g) in methanol (30ml) was added lithium hydroxide (0.41g) in water (10ml) which was stirred under nitrogen for 48 hours. The solvent was removed under reduced pressure, the residue was triturated with ether and filtered to leave lithium 4-{[1-(3,4-dichlorobenzyl)-4-piperidinyl]amino}-4-oxobutanoate (3.50g).

15

Step iii: 3-[3-(4-Bromo-1-methyl-1*H*-pyrazol-3-yl)-1,2,4-oxadiazol-5-yl]-*N*-[1-(3,4-dichlorobenzyl)-4-piperidinyl]propanamide

To lithium 4-{[1-(3,4-dichlorobenzyl)-4-piperidinyl]amino}-4-oxobutanoate

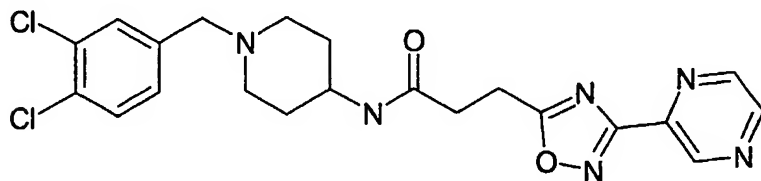
20 (0.292g) in dichloromethane (6ml) was added dimethylformamide (1.5ml), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (0.183g), 1-hydroxybenzotriazole hydrate (0.130g), 4-bromo-*N*-hydroxy-1-methyl-1*H*-pyrazole-3-carboximidamide (0.175g) and triethylamine (0.161g). Reaction was left to stir for 24 hours before removal of dichloromethane under reduced pressure. Pyridine (5ml) was added and heated at reflux for 5 hours. Pyridine was removed under reduced pressure, followed by the addition of water. The solution was extracted three times with dichloromethane. The pooled organic phase was washed once with water, once with saturated brine and dried over magnesium sulfate. After filtration the product was

25

azeotroped twice with toluene and was purified by reverse phase hplc (RPHPLC; 75%-5%, 0.1% ammonium acetate/ acetonitrile). Solvent was removed under reduced pressure to give the titled compound (0.164g).

Example 352

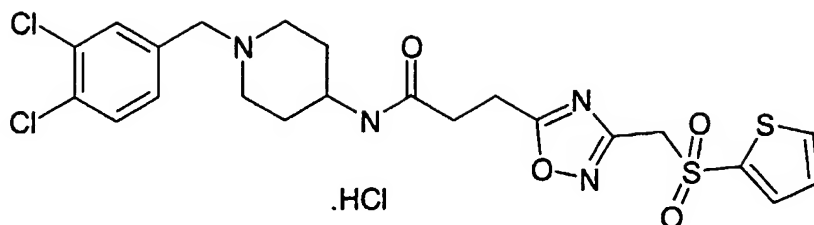
5 *N*-[1-(3,4-Dichlorobenzyl)-4-piperidinyl]-3-[3-(2-pyrazinyl)-1,2,4-oxadiazol-5-yl]propanamide



To lithium 4-[[1-(3,4-dichlorobenzyl)-4-piperidinyl]amino]-4-oxobutanoate (Example 351, step ii) (0.292g) in dichloromethane (6ml) was added *N,N*-dimethylformamide (1.5ml), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (0.183g), 1-hydroxybenzotriazole hydrate (0.130g), *N*'-hydroxy-2-pyrazinecarboximidamide (0.110g) and triethylamine (0.161g). The reaction mixture was left to stir for 24 hours before removal of dichloromethane under reduced pressure. Pyridine (5ml) was added and heated at reflux for 5 hours. Pyridine was removed under reduced pressure followed by the addition of water. The solution was extracted three times with dichloromethane. The pooled organic phase was washed once with water, once with saturated brine and dried over magnesium sulfate. After filtration the product was azeotroped twice with toluene and was purified by RPHPLC (75%-5%, 0.1% ammonium acetate/ acetonitrile). Solvent was removed under reduced pressure to give the title compound (0.067g).

Example 353

N-[1-(3,4-Dichlorobenzyl)-4-piperidinyl]-3-{3-[(2-thienylsulfonyl)methyl]-1,2,4-oxadiazol-5-yl}propanamide hydrochloride



Step i: 3-{3-[(2-Thienylsulfonyl)methyl]-1,2,4-oxadiazol-5-yl}propanoic acid

(1Z)-N'-hydroxy-2-(2-thienylsulfonyl)ethanimidamide (0.250g) with dihydro-2,5-furandione (0.114g) in dimethylformamide (0.2ml) was heated at 120°C for 2 hours. The reaction was allowed to cool and triturated with diethyl ether and filtered to leave 3-{3-[(2-thienylsulfonyl)methyl]-1,2,4-oxadiazol-5-yl}propanoic acid (0.332g).

Step ii: N-[1-(3,4-Dichlorobenzyl)-4-piperidinyl]-3-{3-[(2-thienylsulfonyl)methyl]-1,2,4-oxadiazol-5-yl}propanamide hydrochloride

3-{3-[(2-Thienylsulfonyl)methyl]-1,2,4-oxadiazol-5-yl}propanoic acid (0.332g) in dichloromethane was stirred under nitrogen. Oxalyl chloride (0.252g) was added dropwise followed by the addition of one drop of dimethylformamide. After 30 minutes the solvent and oxalyl chloride was removed under reduced pressure followed by the addition of dichloromethane (10ml), 1-(3,4-dichlorobenzyl)-4-piperidinamine hydrochloride (0.347g), and triethylamine (0.202g) and allowed to stir for 2 hours under nitrogen. Saturated sodium hydrogen carbonate was added to the reaction with the resulting solution being extracted three times with dichloromethane. The pooled organic phases were washed once with water, once with brine, dried over magnesium sulfate, filtered and the solvent removed under reduced pressure to leave a brown oil. This oil was purified by RPHPLC (75%-5%, 0.1% ammonium acetate/ acetonitrile) followed by chromatography using 3% ethanol/ dichloromethane. The solvent was removed under reduced pressure, followed by the addition of hydrogen chloride in diethyl ether, filtered and dried to leave N-[1-(3,4-dichlorobenzyl)-4-piperidinyl]-3-{3-[(2-thienylsulfonyl)methyl]-1,2,4-oxadiazol-5-yl}propanamide hydrochloride (0.04g) as a pale yellow solid.

Example 354

N-[1-(3,4-Dichlorobenzyl)-4-piperidinyl]-3-[3-(4-pyridinyl)-1,2,4-oxadiazol-5-yl]propanamide

Step i: 3-[3-(4-Pyridinyl)-1,2,4-oxadiazol-5-yl]propanoic acid

N-hydroxy-4-pyridinecarboximideamide (0.300g) with dihydro-2,5-furandione (0.217g) in dimethylformamide (2 drops) was heated for 4 times 30 seconds in a CEM MARS 5 microwave at 100% of 300W to leave a fused mass. The reaction was allowed to cool and triturated with ethanol and filtered to leave 3-[3-(4-pyridinyl)-1,2,4-oxadiazol-5-yl]propanoic acid (0.241g).

Step ii: *N*-[1-(3,4-Dichlorobenzyl)-4-piperidinyl]-3-[3-(4-pyridinyl)-1,2,4-oxadiazol-5-yl]propanamide

For method refer to Example 353 step ii. Purification was performed via chromatography (2.5% ethanol/ dichloromethane). Solvent removed under reduced pressure to leave *N*-[1-(3,4-dichlorobenzyl)-4-piperidinyl]-3-[3-(4-pyridinyl)-1,2,4-oxadiazol-5-yl]propanamide (0.154g) as a pale cream solid.

Example 355

Cis-N-[1-(3,4-dichlorobenzyl)-4-piperidinyl]-2-[3-(2-pyridinyl)-1,2,4-oxadiazol-5-yl]cyclopropanecarboxamide

Step i: *Cis*-2-[3-(2-pyridinyl)-1,2,4-oxadiazol-5-yl]cyclopropanecarboxylic acid

N-hydroxy-2-pyridinecarboximidamide (0.137g) with 3-oxabicyclo[3.1.0]hexane-2,4-dione (0.112g) in dimethylformamide (2 drops) was heated for 4 times 30 seconds in a CEM MARS 5 microwave at 100% of 300W to leave a fused mass. The reaction was allowed to cool and triturated with diethyl ether and filtered to leave *cis*-2-[3-(2-pyridinyl)-1,2,4-oxadiazol-5-yl]cyclopropanecarboxylic acid (0.200g).

Step ii: *Cis-N*-[1-(3,4-dichlorobenzyl)-4-piperidinyl]-2-[3-(2-pyridinyl)-1,2,4-oxadiazol-5-yl]cyclopropanecarboxamide

Cis-2-[3-(2-pyridinyl)-1,2,4-oxadiazol-5-yl]cyclopropanecarboxylic acid (0.139g) and *N,N'*-carbonyldiimidazole (0.110g) in dichloromethane was stirred under nitrogen for 1 hour. 1-(3,4-dichlorobenzyl)-4-piperidinamine hydrochloride (0.198g), and triethylamine (0.121g) was then added and allowed to stir for 24 hours under nitrogen. Saturated sodium hydrogen carbonate was added to the reaction with the resulting solution being extracted three times with dichloromethane. The pooled organic phases were washed once with water, once with brine, dried over magnesium sulfate, filtered and the solvent removed under reduced pressure to leave an oil. This oil was purified by RPHPLC (75%-5%, 0.1% ammonium acetate/ acetonitrile). The solvent was removed under reduced pressure to

leave *Cis-N*-[1-(3,4-dichlorobenzyl)-4-piperidiny]-2-[3-(2-pyridinyl)-1,2,4-oxadiazol-5-yl]cyclopropanecarboxamide (0.054g) as a white solid.

Example 356

N-[1-(3,4-Dichlorobenzyl)-4-piperidiny]-3-[3-(2-pyridinyl)-1*H*-1,2,4-triazol-5-yl]propanamide

Step i: 3-[3-(2-Pyridinyl)-1*H*-1,2,4-triazol-5-yl]propanoic acid

2-Pyridinecarbohydrazonamide (0.136g) and dihydro-2,5-furandione (0.100g) in 1 ml of dimethylacetamide was heated for 10 times 30 seconds in a CEM MARS 5 microwave at 100% of 300W under nitrogen to leave 3-[3-(2-pyridinyl)-1*H*-1,2,4-triazol-5-yl]propanoic acid in 1ml of dimethylacetamide.

Step ii: *N*-[1-(3,4-Dichlorobenzyl)-4-piperidiny]-3-[3-(2-pyridinyl)-1*H*-1,2,4-triazol-5-yl]propanamide

3-[3-(2-Pyridinyl)-1*H*-1,2,4-triazol-5-yl]propanoic acid (0.218g in 1ml dimethylacetamide) and *N,N'*-carbonyldiimidazole (0.250g) in dichloromethane was stirred under nitrogen for 30 minutes. 1-(3,4-Dichlorobenzyl)-4-piperidinamine hydrochloride (0.316g), and triethylamine (0.218g) was then added and allowed to stir for 2 hours under nitrogen. 1M sodium hydroxide was added to the reaction with the resulting solution being washed three times with dichloromethane. The aqueous phase was acidified with glacial acetic acid, with the water/ acetic acid being removed under reduced pressure.

Water was then added and extracted three times with dichloromethane. The pooled organic phases were extracted once with water and the water removed under reduced pressure to leave a white solid. This was then triturated with diethyl ether/ dichloromethane, filtered and was purified by RPHPLC (75%-5%, 0.1% ammonium acetate/ acetonitrile), solvent removed to leave *N*-[1-(3,4-dichlorobenzyl)-4-piperidiny]-3-[3-(2-pyridinyl)-1*H*-1,2,4-triazol-5-yl]propanamide (0.02g).

Example 357

N-[1-(3,4-Dichlorobenzyl)-4-piperidiny]-2-(3-phenyl-1*H*-1,2,4-triazol-5-yl)acetamide

(3-Phenyl-1*H*-1,2,4-triazol-5-yl)acetic acid (0.020g) and *N,N'*-carbonyldiimidazole (0.016g) in dichloromethane was stirred under nitrogen for 30 minutes. 1-(3,4-Dichlorobenzyl)-4-piperidinamine hydrochloride (0.031g) and triethylamine (0.036g) was then added and allowed to stir for 1 hour under nitrogen. Saturated sodium hydrogen carbonate was added to the reaction with the resulting solution being extracted three times

with dichloromethane. The pooled organic phases were washed once with water, once with brine, dried over magnesium sulfate, filtered and the solvent removed under reduced pressure to a white solid. This was purified by RPHPLC (75%-5%, 0.1% ammonium acetate/ acetonitrile). Saturated sodium hydrogen carbonate was added to the pooled collected fractions with the resulting solution being extracted three times with dichloromethane. The pooled organic phases were washed once with water, once with brine, dried over magnesium sulfate, filtered and the solvent removed under reduced pressure to leave *N*-[1-(3,4-dichlorobenzyl)-4-piperidinyl]-2-(3-phenyl-1*H*-1,2,4-triazol-5-yl)acetamide(0.031g).

Example 358

N-[1-(3,4-Dichlorobenzyl)-4-piperidinyl]-2-(5-phenyl-1,3,4-oxadiazol-2-yl)acetamide acetate

3-(5-Phenyl-1,3,4-oxadiazol-2-yl)propanoic acid (0.175g) and *N,N'*-carbonyldiimidazole (0.148g) in dichloromethane was stirred under nitrogen for 30 minutes. 1-(3,4-Dichlorobenzyl)-4-piperidinamine hydrochloride (0.263g), and triethylamine (0.126g) was then added and allowed to stir for 2 hours under nitrogen. Saturated sodium hydrogen carbonate was added to the reaction, with the resulting solution being extracted three times with dichloromethane. The pooled organic phases were washed once with water, once with brine, dried over magnesium sulfate, filtered and the solvent removed under reduced pressure to leave a cream solid. This solid was purified by chromatography using 2.5% ethanol/ dichloromethane. The solvent was removed under reduced pressure and was purified by RPHPLC (75%-5%, 0.1% ammonium acetate/ acetonitrile), followed by 1 ml of glacial acetic acid being added and the solvent removed under reduced pressure to leave *N*-[1-(3,4-dichlorobenzyl)-4-piperidinyl]-2-(5-phenyl-1,3,4-oxadiazol-2-yl)acetamide acetate (0.024g).

Example 359

N-[1-(3,4-Dichlorobenzyl)-4-piperidinyl]-2-[3-(2-pyridinyl)-1,2,4-oxadiazol-5-yl]acetamide

Step i: Lithium [3-(2-pyridinyl)-1,2,4-oxadiazol-5-yl]acetate

2-(5-Methyl-1,2,4-oxadiazol-3-yl)pyridine (0.150g) was stirred at -78°C in dry tetrahydrofuran under nitrogen. (1.6M) *n*-butyl lithium (0.757ml) was added dropwise so as to maintain the temperature at -78°C. After 30 minutes carbon dioxide was passed

through the solution and the reaction was allowed to return to room temperature. Once the reaction had reached room temperature, water (1ml) was added and all solvents were removed under reduced pressure to leave a yellow solid. This solid was triturated with ethyl acetate and filtered to leave a pale yellow solid (0.150g).

5 Step ii: *N*-[1-(3,4-Dichlorobenzyl)-4-piperidinyl]-2-[3-(2-pyridinyl)-1,2,4-oxadiazol-5-yl]acetamide

Lithium [3-(2-pyridinyl)-1,2,4-oxadiazol-5-yl]acetate (0.140g), 1-(3,4-dichlorobenzyl)-4-piperidinamine (0.170g), PyBroP™ (0.400g) were stirred under nitrogen in dimethylformamide (15ml). *N,N*-Diisopropylethylamine (0.171g) was added and left to
10 stir for 2 hours. 1M sodium hydroxide was added to the reaction, with the resulting solution being extracted three times with dichloromethane. The pooled organic phases were washed once with water, once with brine, dried over magnesium sulfate, filtered and the solvent removed under reduced pressure to leave product plus dimethylformamide. Water was added which resulted in precipitation of the product. The product was filtered
15 and was purified by RPHPLC (75%-5%, 0.1% ammonium acetate/ acetonitrile). After removal of the solvent under reduced pressure the resulting white solid was triturated with diethyl ether, filtered and dried to leave *N*-[1-(3,4-dichlorobenzyl)-4-piperidinyl]-2-[3-(2-pyridinyl)-1,2,4-oxadiazol-5-yl]acetamide (0.067g; m.p. 145°C).

Example 360

20 *N*-[1-(4-Bromobenzyl)-4-piperidinyl]-2-(4-fluorophenyl)acetamide

2-(4-Fluorophenyl)-*N*-(4-piperidinyl)acetamide (WO97/36871; 1.00g), 1-bromo-4-(bromomethyl)benzene (1.06g) and potassium carbonate (0.877g) in dimethylformamide (15ml) were heated to 70°C, under nitrogen for 1 hour. Water was added to the reaction, with the resulting solution being extracted three times with dichloromethane. The pooled
25 organic phases were washed once with water, once with brine, dried over magnesium sulfate, filtered and the solvent removed under reduced pressure to leave a cream solid. This solid was triturated with diethyl ether, filtered and recrystallised from ethanol/ water to give white crystalline needles of *N*-[1-(4-bromobenzyl)-4-piperidinyl]-2-(4-fluorophenyl)acetamide (m.p. 144°C).

30

Example 361

N-[1-(2-quinolinylmethyl)-4-piperidinyl]-2-(4-fluorophenyl)acetamide

2-(4-Fluorophenyl)-*N*-(4-piperidinyl)acetamide (WO97/36871; 0.05g), 2-quinolinecarbaldehyde (0.033g) and sodium triacetoxyborohydride (0.067g) in dichloroethane (3ml) were stirred under nitrogen for 24 hours. Saturated sodium hydrogen carbonate was added to the reaction, with the resulting solution being extracted three times
5 with dichloromethane. The pooled organic phases were washed once with water, once with brine, dried over magnesium sulfate, filtered and the solvent removed under reduced pressure, triturated with diethyl ether/ ethyl acetate and filtered to leave 2-(4-fluorophenyl)-*N*-[1-(2-quinolinylmethyl)-4-piperidinyl]acetamide (0.020g).

Example 362

10 *N*-[1-(3-Chloro-4-fluorobenzyl)-4-piperidinyl]-3-[3-(2-pyridinyl)-1,2,4-oxadiazol-5-yl]propanamide

3-[3-(2-Pyridinyl)-1,2,4-oxadiazol-5-yl]propanoic acid (0.218g) and *N,N'*-carbonyldiimidazole (0.194g) were stirred in dichloromethane (10ml) under nitrogen for 1 hour. 1-(3-Chloro-4-fluorobenzyl)-4-piperidinamine (JP 59101483; 0.242g) was then
15 added and left to stir for 24 hours. Saturated sodium hydrogen carbonate was added to the reaction, with the resulting solution being extracted three times with dichloromethane. The pooled organic phases were washed once with water, once with brine, dried over magnesium sulfate, filtered and the solvent removed under reduced pressure, triturated with ethyl acetate/ ethanol and filtered to leave *N*-[1-(3-chloro-4-fluorobenzyl)-4-
20 piperidinyl]-3-[3-(2-pyridinyl)-1,2,4-oxadiazol-5-yl]propanamide (m.p. 150°C).

Example 363

N-[1-(4-Chloro-3-fluorobenzyl)-4-piperidinyl]-3-[3-(2-pyridinyl)-1,2,4-oxadiazol-5-yl]propanamide

Step i: *tert*-Butyl 1-(4-chloro-3-fluorobenzyl)-4-piperidinylcarbamate

25 4-Chloro-3-fluorobenzaldehyde (0.793g) and *tert*-butyl 4-piperidinylcarbamate (1.00g) were stirred under nitrogen in dried tetrahydrofuran (25ml). Sodium triacetoxyborohydride (1.266g) was then added and left for 24 hours. Saturated sodium hydrogen carbonate was added to the reaction, with the resulting solution being extracted three times with dichloromethane. The pooled organic phases were washed once with
30 water, once with brine, dried over magnesium sulfate, filtered and the solvent removed under reduced pressure to leave *tert*-butyl 1-(4-chloro-3-fluorobenzyl)-4-piperidinylcarbamate (1.80g) as a white solid.

Step ii: 1-(4-Chloro-3-fluorobenzyl)-4-piperidinamine

tert-Butyl 1-(4-chloro-3-fluorobenzyl)-4-piperidinylcarbamate (1.80g) in dichloromethane (20ml) was stirred under nitrogen. Trifluoroacetic acid (5ml) was then added dropwise and the reaction was left to stir for 2 hours. 1M sodium hydroxide was added to the reaction until basic, with the resulting solution being extracted three times with dichloromethane. The pooled organic phases were washed once with water, once with brine, dried over magnesium sulfate, filtered and the solvent removed under reduced pressure. Product purified by chromatography (5% ethanol/ dichloromethane to 10% ethanol/ dichloromethane) and solvent removed under reduced pressure to leave an oil which crystallised over the period of 48 hours. The resulting solid was triturated with diethyl ether and filtered to leave 1-(4-chloro-3-fluorobenzyl)-4-piperidinamine (0.500g) as a white solid.

Step iii: N-[1-(4-Chloro-3-fluorobenzyl)-4-piperidinyl]-3-[3-(2-pyridinyl)-1,2,4-oxadiazol-5-yl]propanamide

3-[3-(2-Pyridinyl)-1,2,4-oxadiazol-5-yl]propanoic acid (0.136g) and N,N'-carbonyldiimidazole (0.114g) were stirred in dichloromethane (10ml) under nitrogen for 1 hour. 1-(4-Chloro-3-fluorobenzyl)-4-piperidinamine (0.150g) was then added and left to stir for 2 hours. Saturated sodium hydrogen carbonate was added to the reaction, with the resulting solution being extracted three times with dichloromethane. The pooled organic phases were washed once with water, once with brine, dried over magnesium sulfate, filtered and the solvent removed under reduced pressure to leave an oil. This was triturated with diethyl ether which caused product to crystallise. After filtration, the product was washed with diethyl ether and dried to N-[1-(4-chloro-3-fluorobenzyl)-4-piperidinyl]-3-[3-(2-pyridinyl)-1,2,4-oxadiazol-5-yl]propanamide (m.p. 132°C).

Example 364

2-(4-Chlorophenoxy)-N-[1-[(3,4-dichlorophenyl)methyl]-piperidin-4-yl]-acetamide

The product from Example A step (ii) was dissolved in dichloromethane (10ml) containing triethylamine (0.081g) and the solution was cooled to 0°C. 4-Chlorophenoxyacetyl chloride (88mg) in dichloromethane (3ml) was added dropwise, the cooling bath was removed and the resulting solution was stirred for 1 hour. Ethyl acetate, water and brine were added and the phases were separated. The organic phase was dried, filtered and evaporated to give an oil which was purified by reverse phase HPLC (with a

gradient eluent system (25% MeCN/NH₄OAc_{aq} (0.1%) to 95% MeCN/NH₄OAc_{aq} (0.1%)) to give the title compound (0.049g).

Example 365

N-(1-benzyl-4-piperidiny)-3-[3-(2-pyridinyl)-1,2,4-oxadiazol-5-yl]propanamide

5 To a solution of 3-(3-pyridin-2-yl-[1,2,4]oxadiazol-5-yl)-propionic acid (1g) in tetrahydrofuran (5ml), was added carbonyldiimidazole (0.74g). The mixture was stirred for 10 minutes before addition of 1-benzyl-piperidin-4-ylamine (1ml) in tetrahydrofuran (5ml). The reaction mixture was stirred for 15 minutes then partitioned between ethyl acetate (20ml) and water (20ml). The organic layer was separated, dried (MgSO₄) and
10 solvent removed by evaporation. Purification by Biotage® 40S eluting 3%MeOH/0.5% 880 ammonia/dichloromethane gave the title compound (0.93g).

Example 366

N-(2-{[1-(3,4-Dichloro-benzyl)-piperidin-4-yl]-methyl-amino}-ethyl)-2-(2-fluoro-phenyl)-acetamide

15 Step i: (2-Methylamino-ethyl)-carbamic acid tert -butyl ester

To a solution of (2-amino-ethyl)-carbamic acid-*tert*-butyl ester (5g) and triethylamine (6.5ml) in tetrahydrofuran (1000ml) at 0°C was added methyl iodide (1.94ml) dropwise over a period of 1 hour. The mixture was allowed to warm to ambient temperature and stirred for 72 hours before removal of solvents by evaporation. The
20 residue was partitioned between ethyl acetate and water. The organic layer was separated, dried (MgSO₄) and solvent removed by evaporation to give the title compound (3.7g).

Step ii: (2-{[1-(3,4-Dichloro-benzyl)-piperidin-4-yl]-methyl-amino}-ethyl)-carbamic acid *tert*-butyl ester

To a solution of dichlorobenzyl- piperidin-4-one (Example 74, step (i), 4.8g) and
25 acetic acid (1ml) in dichloromethane (100ml) was added (2-methylamino-ethyl)-carbamic acid *tert*-butyl ester (3.26g) and the mixture was stirred for 5 minutes before addition of sodium triacetoxyborohydride (7.9g). The reaction mixture was stirred for 12 hours before addition of sodium bicarbonate solution. The mixture was stirred for ½ hour and then partitioned between water and dichloromethane. The organic layer was separated, dried
30 (MgSO₄) and solvent removed by evaporation. Purification by Biotage® 40S eluting 10%MeOH/2% triethylamine/dichloromethane gave the title compound (1.7g).

Step iii: *N*¹-[1-(3,4-Dichloro-benzyl)-piperidin-4-yl]-*N*¹-methyl-ethane-1,2-diamine

(2-{{1-(3,4-Dichloro-benzyl)-piperidin-4-yl}-methyl-amino}-ethyl)-carbamic acid *tert*-butyl ester (1.7g) was dissolved in 6M HCl (20ml) and stirred for 12 hours. The solvent was evaporated and the residue was azeotroped with toluene and then sodium bicarbonate solution was added. The mixture was stirred for 10 minutes and the product
5 was extracted with dichloromethane. The solvent was removed by evaporation to give the title compound (0.75g).

Step iv: *N*-(2-{{1-(3,4-Dichloro-benzyl)-piperidin-4-yl}-methyl-amino}-ethyl)-2-(2-fluorophenyl)-acetamide

Prepared by the method of Example 359 step (ii) using *N*¹-[1-(3,4-Dichloro-benzyl)-piperidin-4-yl]-*N*¹-methyl-ethane-1,2-diamine and 2-fluorophenylacetic acid.
10

Example 367

N-[1-(3,4-dichlorobenzyl)-4-piperidinyl]-*N*-methyl-2-(4-fluorophenyl)acetamide

Step i: [1-(3,4-Dichlorobenzyl)-piperidin-4-yl]-methyl-amine

To a solution of 1-(3,4-Dichloro-benzyl)-piperidin-4-one (3.1g) in dichloromethane
15 (50ml) and acetic acid (0.69ml) was added methylamine (6ml of a 1M solution in tetrahydrofuran). The mixture was stirred for 5 minutes before the addition of sodium triacetoxymethylborohydride (3g) and the resulting mixture stirred for 72 hours. Sodium bicarbonate solution (100ml) added and the mixture stirred vigorously for 5 minutes before extraction of the product with dichloromethane (2X200ml). The organics were separated,
20 bulked and dried, (MgSO₄). Purification by Biotage® 40S eluting 10%MeOH/0.5% 880 ammonia/dichloromethane gave the sub-title compound (1.8g).

Step ii: *N*-[1-(3,4-dichlorobenzyl)-4-piperidinyl]-2-(4-fluorophenyl)acetamide

To a solution of 4-fluorophenylacetic acid (100mg) in tetrahydrofuran (3ml) was added carbonyldiimidazole (105mg). The mixture was stirred for 10 minutes before
25 addition of [1-(3,4-dichlorobenzyl)-piperidin-4-yl]-methyl-amine (177mg) in tetrahydrofuran (2ml). Stirring was continued for 1 hour then solvent removed by evaporation. Purification by Biotage® 40S eluting 2%MeOH/0.5% 880 ammonia/dichloromethane gave the title compound (166mg).

Example 368

30 *N*-[1-[(3,4-dichlorophenyl)methyl]-4-piperidinyl]-2-(2-pyrimidinyl)-acetamide

Step i: Ethyl 2-pyrimidinylacetate

Ethyl glycolate (1.04g) was dissolved in tetrahydrofuran (10ml) and the solution was cooled to 0°C. Sodium hydride (60% suspension in oil, 0.43g) was added and the suspension was stirred and then sonicated in an ultrasonic bath. 2-Chloropyrimidine (1.14g) was added and the mixture was sonicated for a further 110min. Ammonium chloride solution was added and the mixture was extracted thrice with ethyl acetate, the organic phases were washed with brine and dried, filtered and evaporated. The residue was purified by chromatography eluting with *iso*-hexane: ethyl acetate (13:7) to give the subtitle compound (1.40g) as an oil.

Step ii: 2-Pyrimidininyloxyacetic acid

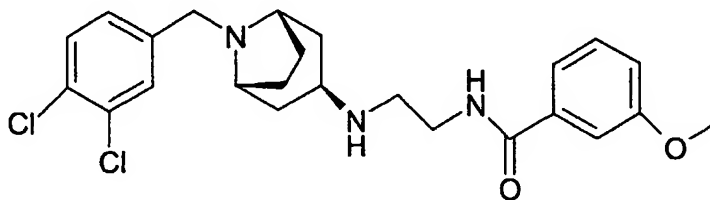
Ethyl 2-pyrimidininyloxyacetate (1.4g) was dissolved in ethanol (10ml). Sodium hydroxide (2M aq) was added and the mixture was stirred for 64h. The solvent was evaporated and the residue was dissolved in water, filtered and the acidified with concentrated hydrochloric acid. The resulting precipitate was collected and dried to give the subtitle compound (0.698g).

Step iii: *N*-[1-[(3,4-dichlorophenyl)methyl]-4-piperidinyl]-2-(2-pyrimidininyloxy)-acetamide

The title compound was prepared from the product of Example A step (ii) (hydrochloride salt, 335mg) and 2-pyrimidininyloxyacetic acid (170mg) using the method of Example 94. Yield 140mg, m.p. 120-122°C.

Example 369

N-[2-[[8-[(3,4-Dichlorophenyl)methyl]-8-azabicyclo[3.2.1]oct-3-yl]amino]ethyl]-3-methoxy-benzamide, bis toluene sulfonic acid salt



Step i: 8-[(3,4-Dichlorophenyl)methyl]-8-azabicyclo[3.2.1]octan-3-one

2,5-Dimethoxytetrahydrofuran (4.92g) was stirred in hydrochloric acid (1M, 25 ml) for 1 hour. 3,4-Dichlorobenzylamine (5ml) was added to hydrochloric acid (1M, 15ml) and the resulting suspension was added to the first solution. Phosphate buffer solution (pH 5.5, 250ml) was added followed by sodium hydroxide (1.6g). A solution of acetone

dicarboxylic acid (4.77g) in phosphate buffer solution (pH 5.5, 90ml) was added to the mixture and the solution was stirred. A yellow solid formed and the mixture was left to stand for 64h. The aqueous supernatant was decanted and hydrochloric acid (2.5M) was added to the solid along with ethyl acetate. The layers were separated and the aqueous phase was extracted twice with dichloromethane containing a little methanol. The organic layers were combined and evaporated to give a crude oil (ca 7g). A portion of the product (ca 2.5g) was purified by chromatography eluting with dichloromethane : methanol (19:1) to give the subtitle compound (1.62g) as a yellow oil.

Step ii: Carbamic acid, Endo-[2-[[8-[(3,4-dichlorophenyl)methyl]-8-azabicyclo[3.2.1]oct-3-yl]amino]ethyl]-1,1-dimethylethyl ester

8-[(3,4-Dichlorophenyl)methyl]-8-azabicyclo[3.2.1]octan-3-one (751 mg) and carbamic acid, (2-aminoethyl)-1,1-dimethylethyl ester (520 mg) were dissolved in dichloroethane (23ml). Sodium triacetoxyborohydride (697 mg) was added and the suspension was stirred at room temperature for 20hours. Dichloromethane was added and the solution was washed with sodium bicarbonate solution, then with water and then with brine. Chromatography of the residue eluting with ethyl acetate : methanol : triethylamine (80:19:1) gave the subtitle compound (688mg) as an oil.

Step iii: *N*-[2-[[8-[(3,4-Dichlorophenyl)methyl]-8-azabicyclo[3.2.1]oct-3-yl]amino]ethyl]-3-methoxy-benzamide, bis toluene sulfonic acid salt

Carbamic acid, [2-[[8-[(3,4-dichlorophenyl)methyl]-8-azabicyclo[3.2.1]oct-3-yl]amino]ethyl]-, 1,1-dimethylethyl ester (337mg) was dissolved in dichloromethane (3ml) and trifluoroacetic acid (3ml) was added. The resulting solution was stirred for 1 hour then the volatiles were evaporated. The residue was dissolved in dichloromethane (3ml) and triethylamine (1ml) was added followed by 3-methoxybenzoyl chloride (120μl). The solution was stirred overnight. The solvent was evaporated and the residue was purified by RPHPLC (gradient ammonium acetate 1% aqueous : acetonitrile (25% acetonitrile to 95% acetonitrile)). Excess tosic acid in ether was added to the residue and the resultant salt was recrystallised from a mixture of ethyl acetate – ethanol with a little cyclohexane to give the title compound (77mg; m.p. 180-182.5°C).

Example 370

Endo-*N*-[8-[(3,4-dichlorophenyl)methyl]-8-azabicyclo[3.2.1]oct-3-yl]-3-(2-pyridinyl)-1,2,4-oxadiazole-5-propanamide hydrochloride

Step i: Endo-8-[(3,4-dichlorophenyl)methyl]-8-azabicyclo[3.2.1]octan-3-amine

8-[(3,4-Dichlorophenyl)methyl]-8-azabicyclo[3.2.1]octan-3-one (350mg) was dissolved in dry methanol (12ml) and ammonium acetate (1g) was added. The mixture was stirred to get partial solution and then sodium cyanoborohydride (106mg) was added.

5 The mixture was heated under reflux for 150 minutes, then allowed to cool to room temperature. The methanol was evaporated, the residue was partitioned between sodium hydroxide and dichloromethane, and the aqueous phase was extracted twice with dichloromethane. The organic phases were combined, dried, filtered and evaporated to give the subtitle compound.

10 Step ii: Endo-*N*-[8-[(3,4-dichlorophenyl)methyl]-8-azabicyclo[3.2.1]oct-3-yl]-3-(2-pyridinyl)-1,2,4-oxadiazole-5-propanamide hydrochloride

3-(2-Pyridinyl)-1,2,4-oxadiazole-5-propanoic acid (305mg) was suspended in dichloromethane (6ml) and oxalyl chloride (0.5ml) was added. The mixture was stirred overnight. Toluene (1ml) was added to the solution, the volatiles were evaporated, then
15 the residue was redissolved in dichloromethane (2ml). Endo-8-[(3,4-dichlorophenyl)methyl]-8-azabicyclo[3.2.1]octan-3-amine (all from step(i)) was dissolved in dichloromethane (4ml) containing triethylamine (0.5ml) and then cooled in an ice bath. The acid chloride solution was added to the amine and the mixture was stirred for 1 hour. Water was added to the reaction mixture and the phases were separated. The aqueous
20 phase was extracted twice with dichloromethane, the organic phases were dried, filtered and evaporated. The residue was purified by RPHPLC (gradient ammonium acetate 1% aqueous : acetonitrile (25% acetonitrile to 95% acetonitrile)). The product was suspended in ether and the ethereal hydrochloric acid was added, the suspension was stirred and then the diethyl ether was evaporated. The residue was dissolved in hot ethyl acetate containing
25 ethanol and crystallisation was induced by adding *iso*-hexane to give the title compound (47mg).

Example 371

2-[4-(acetylamino)phenoxy]-*N*-[1-[(3,4-dichlorophenyl)methyl]-4-piperidinyl]-acetamide

Step i: Methyl (4-acetaminophenoxy)acetate

30 4-Acetaminophenol (1.51g), potassium carbonate (1.38g) and methyl bromoacetate (1.0ml) were combined in acetone (40ml) and heated to reflux for 5 hours. The mixture was allowed to cool to room temperature, filtered and evaporated. The residue was

dissolved in ethyl acetate, washed with water and then with brine then dried, filtered and evaporated to give the subtitle compound (2.32g).

Step ii: (4-Acetaminophenoxy)acetic acid

Methyl (4-acetaminophenoxy)acetate was hydrolysed following the method of
5 Example 368 step (ii) to give the subtitle compound (1.85g).

Step iii: 2-[4-(acetylamino)phenoxy]-*N*-[1-[(3,4-dichlorophenyl)methyl]-4-piperidinyl]-acetamide

The title compound was prepared from the product of Example A step (ii) (free base, 281mg) and (4-acetaminophenoxy)acetic acid (229mg) using a method hereinbefore
10 described (yield 40mg; m.p. 177-178.5°C).

Example 372

N-[1-[(3,4-dichlorophenyl)methyl]-4-piperidinyl]-4-hydroxy- benzeneacetamide

The title compound was prepared from the product of Example A step (ii) (free base, 172mg) and 4-hydroxyphenylacetic acid (135mg) using a method hereinbefore
15 described (yield 57mg; m.p. 72-97°C).

Example 373

Exo-*N*-[8-[(3,4-dichlorophenyl)methyl]-8-azabicyclo[3.2.1]oct-3-yl]-3-(2-pyridinyl)-1,2,4-oxadiazole-5-propanamide

Step i: Endo-8-[(3,4-dichlorophenyl)methyl]-8-azabicyclo[3.2.1]octan-3-ol

20 8-[(3,4-Dichlorophenyl)methyl]-8-azabicyclo[3.2.1]octan-3-one (330mg) was dissolved in tetrahydrofuran (5ml) and cooled to 0°C. Lithium tris (3-ethylpentyl-3-oxy)aluminumhydride solution (0.5M, 2.5ml) was added dropwise and the mixture was allowed to attain room temperature overnight. Sodium sulfate decahydrate (ca 2g) was added and the suspension was stirred for 1hour. The reaction mixture was diluted with
25 ethyl acetate, filtered through kieselguhr and evaporated. The residue was purified by chromatography eluting with dichloromethane: methanol (9:1) to give the subtitle compound 161mg.

Step ii: Exo-2-[8-[(3,4-dichlorophenyl)methyl]-8-azabicyclo[3.2.1]oct-3-yl]-1*H*-isoindole-1,3(2*H*)-dione

30 Endo-8-[(3,4-dichlorophenyl)methyl]-8-azabicyclo[3.2.1]octan-3-ol (556mg), phthalimide (321mg) and polymer bound triphenylphosphine (821mg) were combined in tetrahydrofuran (10ml). Diethylazodicarboxylate (330μl) was added and the mixture was

stirred gently overnight. Additional phosphine (0.5g) and diethylazodicarboxylate (200µl) were added and the mixture was stirred for an additional 5 days. The reaction mixture was diluted with ethyl acetate and filtered; the residue was washed with ethyl acetate and methanol. The filtrate was evaporated, and chromatographed eluting with 9:1 ethyl acetate : methanol. RPHPLC of the product (gradient ammonium acetate 1% aqueous : acetonitrile (25% acetonitrile to 100% acetonitrile)) gave the subtitle compound (90mg).
Step iii: Exo-8-[(3,4-dichlorophenyl)methyl]-8-azabicyclo[3.2.1]octan-3-amine

Exo-2-[8-[(3,4-dichlorophenyl)methyl]-8-azabicyclo[3.2.1]oct-3-yl]-1*H*-isoindole-1,3(2*H*)-dione (90mg) was dissolved in ethanol (6ml) containing dichloromethane (3ml); hydrazine hydrate (0.2ml) was added and the resulting solution was stirred at room temperature for 26 hours. The suspension was filtered and the filtrate was evaporated to give the subtitle compound (55mg).

Step iv: Exo-*N*-[8-[(3,4-dichlorophenyl)methyl]-8-azabicyclo[3.2.1]oct-3-yl]-3-(2-pyridinyl)-1,2,4-oxadiazole-5-propanamide

Prepared following the method of Example 370 step (iii) but without salt formation to give the title compound (15mg; m.p. 177.5-178°C).

Example 374

(*R*) *N*-[1-[1-(4-bromophenyl)ethyl]-4-piperidinyl]-3-(2-pyridinyl)-1,2,4-oxadiazole-5-propanamide

Step i: (*R*)-1-[1-(4-Bromophenyl)ethyl]-4-piperidinone

(*R*)-(4-Bromophenyl)ethylamine (1.01g) and potassium carbonate (1.45g) were dissolved in a mixture of ethanol (13ml) and water (6ml) and then heated to a vigorous reflux. A solution of 4-hydroxy-4-methoxy-1,1-dimethyl-piperidinium iodide (J. Chem. Soc. Perkin Trans. 2, (1984) 1647) (1.47g) in warm water (6ml) was added dropwise over 40 minutes; reflux was maintained for a further 12 hours, then the reaction was allowed to cool to room temperature. The mixture was evaporated and ethyl acetate and water were added and the phases were separated. The aqueous phase was extracted twice with ethyl acetate, the organic layer was washed with brine, dried, filtered and evaporated. Chromatography of the residue eluting with *iso*-hexane : ethyl acetate (3:2) gave the subtitle compound (804mg).

Step ii: (*R*)-1-[1-(4-Bromophenyl)ethyl]-4-piperidinamine

Prepared following the general method of Example 370 step (i) (R)-1-[1-(4-bromophenyl)ethyl]-4-piperidinone (420mg) ammonium acetate (0.80g) and sodium cyanoborohydride (120mg) to give the subtitle compound (449mg).

Step iii: (R) *N*-[1-[1-(4-bromophenyl)ethyl]-4-piperidinyl]-3-(2-pyridinyl)-1,2,4-oxadiazole-5-propanamide

Prepared following a method as hereinbefore described using (R)-1-[1-(4-bromophenyl)ethyl]-4-piperidinamine (449mg), 3-(2-pyridinyl)-1,2,4-oxadiazole-5-propanoic acid (0.31g), 1-hydroxybenzotriazole (0.20g), 4-(*N,N*-dimethylamino)-pyridine (0.13g) and 1-ethyl-3-[3-(dimethylamino)-propyl]carbodiimide hydrochloride (0.30g) to give the title compound (40mg; m.p. 153-155°C).

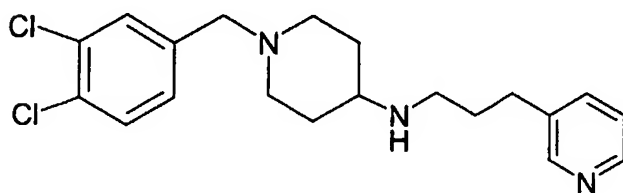
Example 375

(S) *N*-[1-[1-(4-bromophenyl)ethyl]-4-piperidinyl]-3-(2-pyridinyl)-1,2,4-oxadiazole-5-propanamide

Prepared following an analogous series of steps to example 374 but using (S)-(4-bromophenyl)ethylamine to give the title compound. m.p. 141.5-143°C
 $\alpha_D -29.55^\circ$ ($c=0.13$, methanol, 21°C)

Example 385

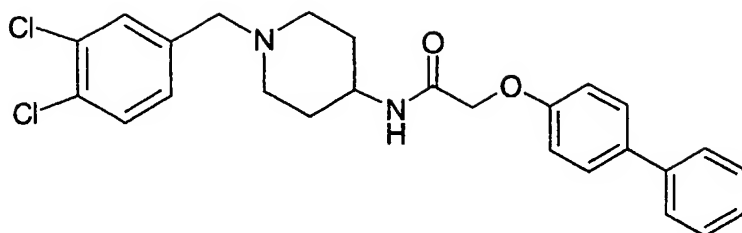
1-[3,4-Dichlorobenzyl]-*N*-[3-(3-pyridinyl)propyl]-4-piperidinamine



The title compound was prepared from 1-(3,4-dichlorobenzyl)piperidine-4-amine (free base 187mg), 3-(3-pyridinyl)propanal (125mg), sodium triacetoxyborohydride (70mg), and 0.02ml acetic acid, stirred together for 2hrs in dichloromethane (10ml). Water was added, the mixture neutralised with sodium bicarbonate and the organic phase separated, dried and chromatographed on silica with ethyl acetate/methanol (9:1) as eluant, to give the title compound (70mg) as a colourless oil.

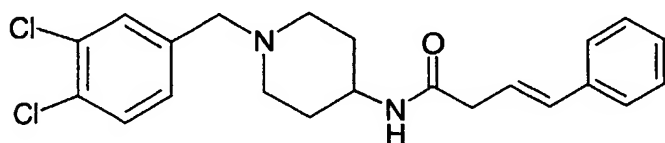
Example 386

2-[(1,1'-Biphenyl)-4-yloxy]-*N*-[1-(3,4-dichlorobenzyl)-4-piperidinyl]acetamide



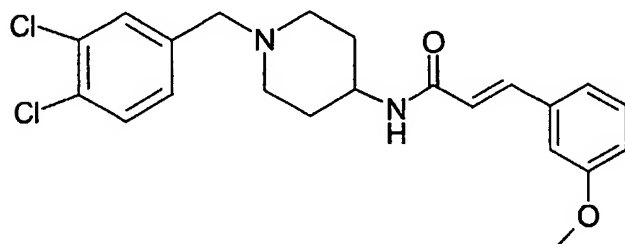
Example 387

N-[1-(3,4-dichlorobenzyl)-4-piperidiny]-4-phenyl-3-butenamide



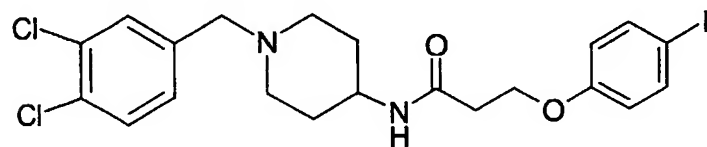
Example 388

N-[1-(3,4-dichlorobenzyl)-4-piperidiny]-3-(3-methoxyphenyl)-2-propenamide.



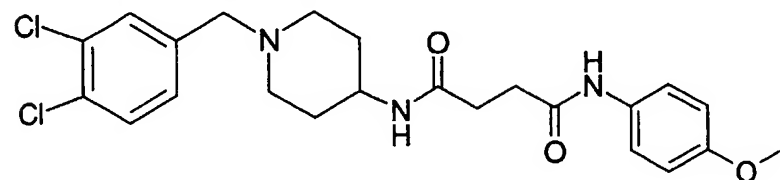
Example 389

N-[1-(3,4-dichlorobenzyl)-4-piperidiny]-3-(4-iodophenoxy)propanamide.



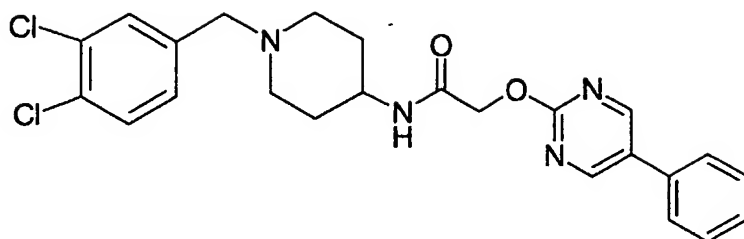
Example 390

N-[1-(3,4-dichlorobenzyl)-4-piperidiny]-N'-(4-methoxyphenyl)succinamide



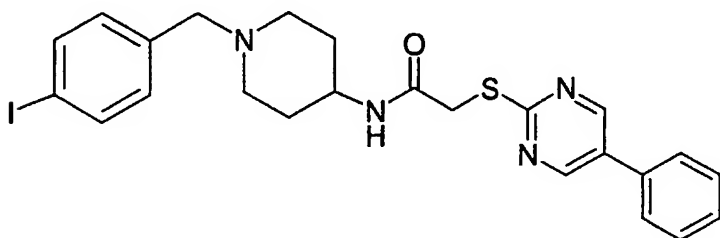
Example 391

N-[1-(3,4-dichlorobenzyl)-4-piperidiny]-2-[(5-phenyl-2-pyrimidinyl)oxy] acetamide



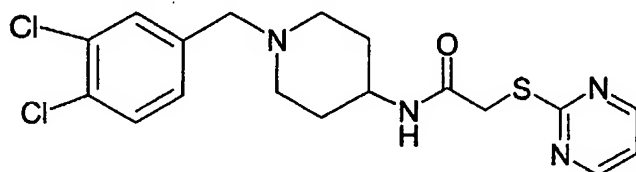
Example 392

N-[1-(4-iodobenzyl)-4-piperidiny]-2-(5-phenyl-2-pyrimidinyl)thioacetamide



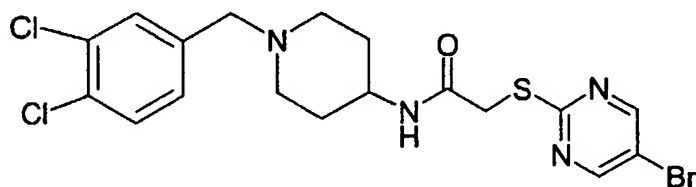
Example 393

N-[1-(3,4-dichlorobenzyl)-4-piperidiny]-2-[(2-pyrimidinyl)thio]acetamide



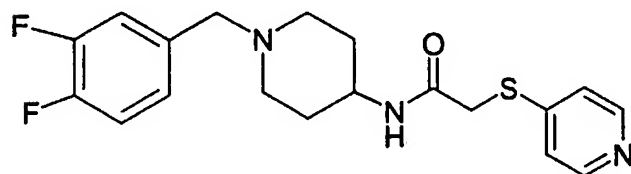
Example 394

2-[(5-Bromo-2-pyrimidinyl)thio]-N-[1-(3,4-dichlorobenzyl)-4-piperidiny]acetamide



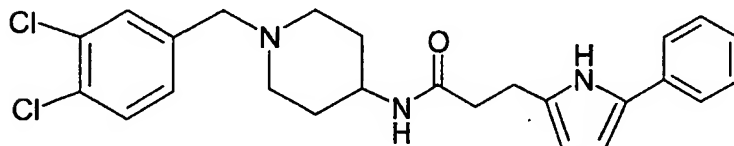
Example 395

N-[1-(3,4-difluorobenzyl)-4-piperidiny]-2-(4-pyridinylthio)acetamide

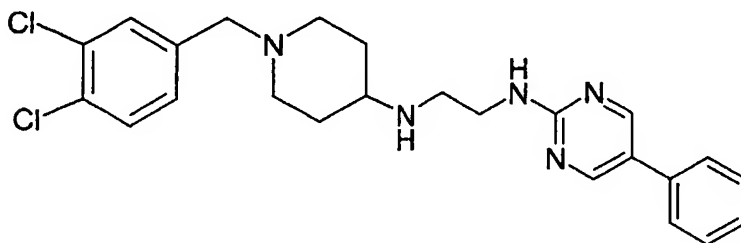


Example 396

N-[1-(3,4-dichlorobenzyl)-4-piperidiny]-3-(5-phenyl-1H-pyrrol-2-yl)propanamide

Example 397

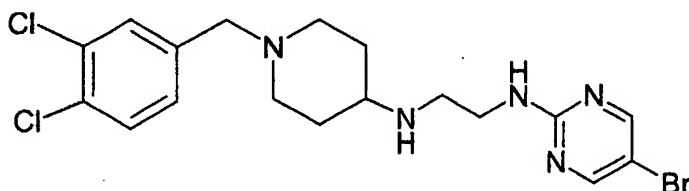
5 N-[1-(3,4-dichlorobenzyl)-4-piperidiny]-N'-(5-phenyl-2-pyrimidinyl)-1,2-ethandiamine



The title compound (20mg) was prepared by heating at reflux *N*'-[1-(3,4-dichlorobenzyl)-4-piperidiny]-1,2-ethanediamine (100mg) and 2-chloro-5-phenypyrimidine (100mg) and Hunigs' base (100mg) in toluene for 8hours. The mixture
10 was purified by chromatography on silica, with ethyl acetate methanol (9:1) as eluant to give the title compound as a yellow oil.

Example 398

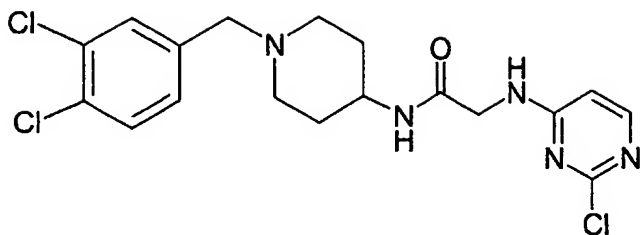
N-[5-bromo-2-pyrimidinyl]-N'-[1-(3,4-dichlorobenzyl)-4-piperidiny]- 1,2-ethandiamine



15 Prepared by the method of Example 397 amine (200mg), 2-chloro-5-bromopyrimidine (130mg), Hunigs' base (200mg) to give the title compound (20mg).

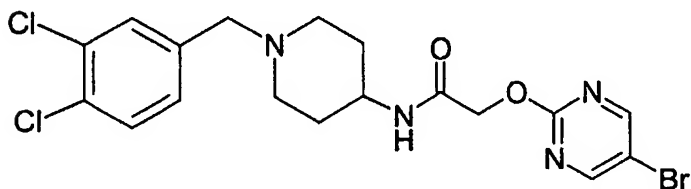
Example 399

2-[(2-Chloro-4-pyrimidinyl)amino]-N-[1-(3,4-dichlorobenzyl)-4-piperidiny] acetamide



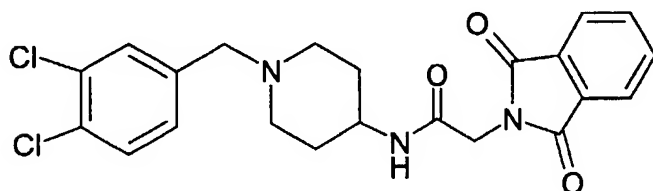
Example 401

2-[(5 -Bromo-2-pyrimidinyl)oxy]-N-[1-(3,4-dichlorobenzyl)-4-piperidyl]-2-acetamide



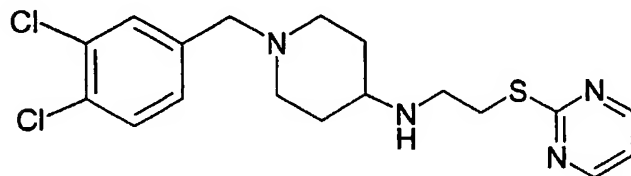
Example 402

N-[1-(3,4-dichlorobenzyl)-4-piperidyl]-2-(1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)acetamide



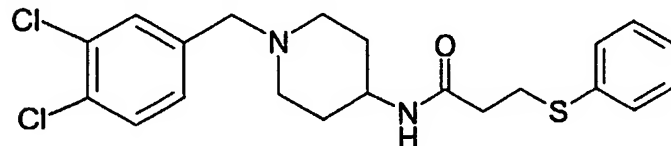
Example 403

N-[1-(3,4-dichlorobenzyl)-4-piperidyl]-N-[2-(2-pyridinylthio)ethylamine, dihydrochloride



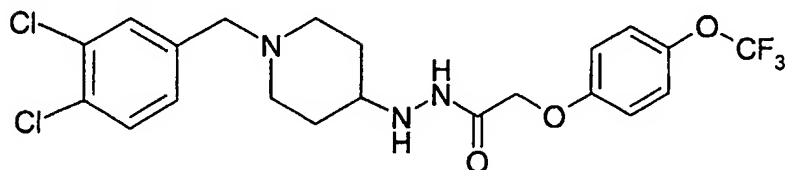
Example 404

N-[1-(3,4-dichlorobenzyl)-4-piperidyl]-3-(phenylthio)propanamide



Example 405

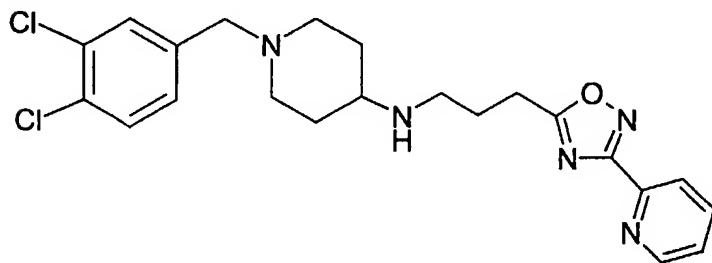
N'-[1-(3,4-dichlorobenzyl)-4-piperidinyl]-2-[4-(trifluoromethoxy)phenoxy]acetohydrazide



- 5 The title compound was prepared from 3,4-dichlorobenzyl-4-piperidone (J. Med. Chem, 1999, 42, 3629; 100mg), 2-[4-(trifluoromethoxy)phenoxy]acetohydrazide (100mg), sodium triacetoxyborohydride (100mg), and 0.02ml acetic acid, stirred together for 2hours in dichloromethane by the method of Example 369 step ii.

Example 406

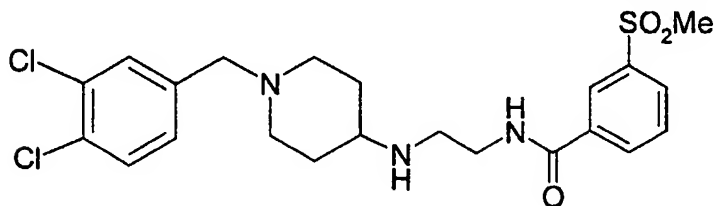
- 10 N-[1-(3,4-dichlorobenzyl)-4-piperidinyl]-N-[3-[3-(2-pyridinyl)-1,2,4-oxadiazol-5-yl]propyl]amine



- The title compound (29mg) was prepared from 3,4-dichlorobenzylpiperidine-4-amine (100mg free base), 2-[5-(3-bromopropyl)-1,2,4-oxadiazol-3-yl]pyridine (100mg), potassium carbonate (100mg) in dimethyl formamide (1ml) were heated together in the microwave for 30secs, water was added and the product extracted into dichloromethane and chromatographed on silica with ethyl acetate/methanol(9:1) as eluant.
- 15

Example 407

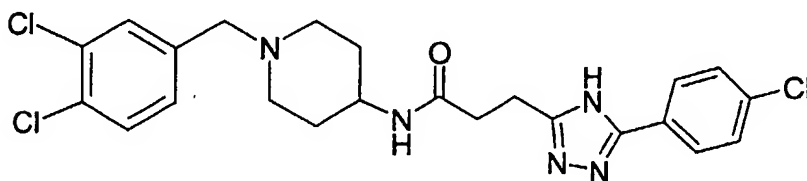
N-[2-[1-(3,4-dichlorobenzyl)-4-piperidinyl]amino]ethyl]-3-(methylsulphonyl)benzamide



Prepared from *N*-(2-aminoethyl)-*N*-[1-(3,4-dichlorobenzyl)-4-piperidiny]-2,2,2-trifluoroacetamide (100mg), 3-methylsulphonylbenzoic acid (50mg) and carbonyldiimidazole (40mg). The product obtained was stirred together with sodium hydroxide (40mg) in 50:50 methanol/ water for 12hrs, extracted into dichloromethane and purified by chromatography on silica with ethyl acetate/methanol (9:1) as eluant, to give the title compound (25mg).

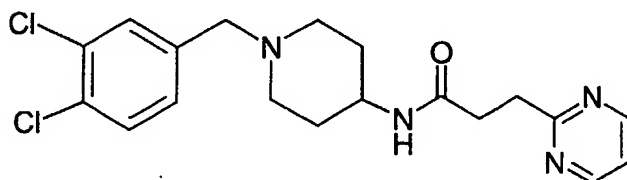
Example 408

3-[5-(4-chlorophenyl)-4H-1,2,4-triazol-3-yl]-*N*-[1-(3,4-dichlorobenzyl)-4-piperidiny]propanamide



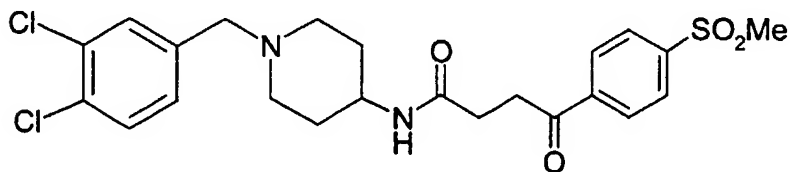
Example 409

N-[1-(3,4-dichlorobenzyl)-4-piperidiny]-3-(2-pyridiny)propanamide



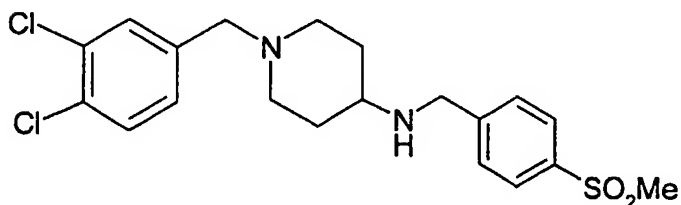
Example 410

N-[1-(3,4-dichlorobenzyl)-4-piperidiny]-4-(4-(methylsulphonyl)phenyl)-4-oxobutanamide



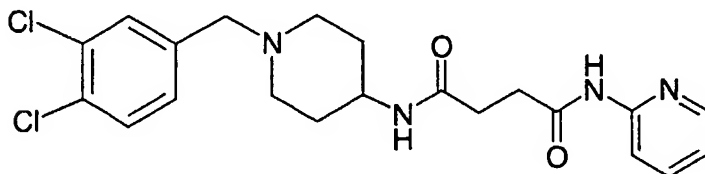
Example 411

N-[1-(3,4-dichlorobenzyl)-4-piperidiny]-*N*'-[4-(methylsulphonyl) benzylamine

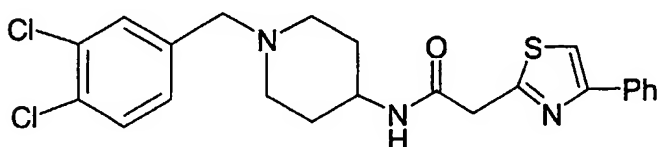


Example 412

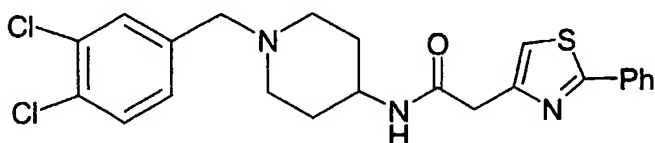
N-[1-(3,4-dichlorobenzyl)-4-piperidiny]-N'-[(2-pyridinyl) succinamide

Example 413

5 N-[1-(3,4-dichlorobenzyl)-4-piperidiny]-2-(4-phenyl-1,3-thiazol-2-yl))acetamide

Example 414

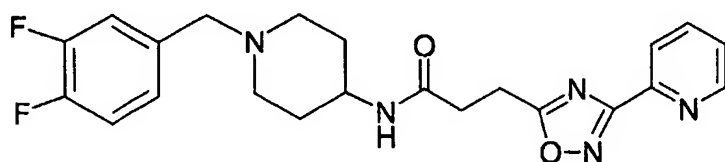
N-[1-(3,4-dichlorobenzyl)-4-piperidiny]-2-(2-phenyl-1,3-thiazol-4-yl))acetamide



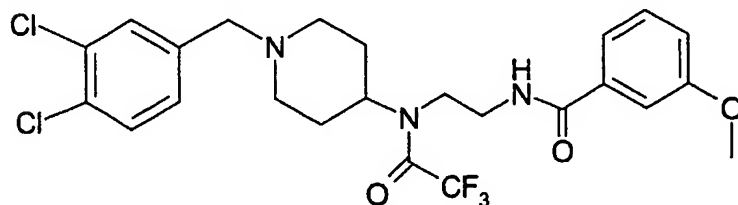
10

Example 415

N-[1-(3,4-difluorobenzyl)-4-piperidiny]-3-(3-(2-pyridinyl-1,2,4-oxadiazol-5-yl)propanamide

Example 416

15 N-trifluoroacetyl-N-[2-[1-(3,4-dichlorobenzyl)-4-piperidiny]amino]ethyl]-3-methoxybenzamide



a) *tert*-butyl 2-{[1-(3,4-dichlorobenzyl)-4-piperidinyl]amino}ethylcarbamate

The sub-title compound (800mg) was prepared from 3,4-dichlorobenzyl-4-piperidone (1.3g) *tert*-butyl 2-aminoethylcarbamate (0.8g), sodium triacetoxyborohydride (100mg), and 0.02ml acetic acid, stirred together for 2hrs in dichloromethane. The sub-

5 titled compound was isolated by standard procedures.

MS [M+H]⁺ (ES+) 402

b) *N*-(2-aminoethyl)-*N*-[1-(3,4-dichlorobenzyl)-4-piperidinyl]-2,2,2-trifluoroacetamide

A mixture of the above amine (800mg), and triethylamine (0.5ml) in dichloromethane (50ml), treated with trifluoroacetic anhydride (420mg) over 30 mins,

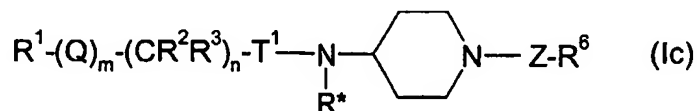
10 evaporated to dryness and dichloromethane(20ml) and trifluoroacetic acid (2ml) added, stirred for 3hrs, then neutralised with aqueous sodium bicarbonate, the organic phase separated, dried and evaporated to give the title compound (250mg) as a yellow oil.

c) *N*-trifluoroacetyl-*N*-[2-[1-(3,4-dichlorobenzyl)-4-piperidinyl]amino]ethyl]-3-methoxybenzamide

15 The title compound (30mg) was prepared from the product above (40mg) 3-methoxybenzoyl chloride (20mg) and triethylamine (50mg) using one of the methods described above.

MS [M+H]⁺ (ES+) 580

20 Further compounds of formula (I), all according to formula (Ic), are shown in the table below.



Example	R ¹	(Q) _m	(CR ² R ³) _n	T ¹	R*	Z	R ⁶
380	4-Cl-C ₆ H ₄	O	CH ₂	C(O)	H	CH ₂ C (O)NH	2-Cl-5- CH ₃ -C ₆ H ₃
381	4-Cl-C ₆ H ₄	O	CH ₂	C(O)	H	(CH ₂) ₃	C ₆ H ₅
382	3-(pyridin-2-yl)- 1,2,4-oxadiazol-5-yl	O	CH ₂	C(O)	H	allyl	C ₆ H ₅
383	2-(cyclopropyl-NH)- pyrimidin-4-yl	m=0	n=0	-	CH ₃	CH ₂	3,4-Cl ₂ - C ₆ H ₃

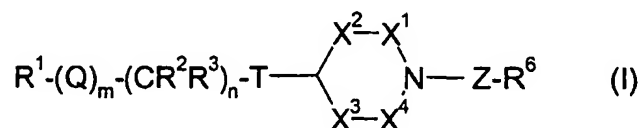
384	2-(pyridin-3-yl)- pyrimidin-4-yl	m=0	n=0	-	CH ₃	CH ₂	3,4-Cl ₂ - C ₆ H ₃
400	pyrimidin-2-yl	S	CH ₂	C(O)	H	C(O)	3,4-Cl ₂ - C ₆ H ₃

EXAMPLE 417

A pharmaceutical combination comprising a compound of formula (I) (such as the
 5 compound of one of Examples 1 to 416; especially the compound of Example 99, 100, 102
 or 415) and loratidine, desloratidine, fexofenadine, cetirizine, ebastine, astemizole,
 norastemizole, epinastine, efletirizine, budesonide, fluticasone, mometasone, rofleponide,
 montelukast, pranlukast, zafirlukast, Z4407, zafirlukast, recombinant human IL-10,
 recombinant human IL-12, formoterol, salmeterol, salbutamol, SB-207499, theophylline,
 10 an anti-IL-5 antibody or an anti-TNF-antibody.

CLAIMS

1. A pharmaceutical combination comprising a compound of formula (I):



5 wherein

Z is CR^4R^5 , $C(O)$ or $CR^4R^5-Z^1$;

Z^1 is C_{1-4} alkylene (such as CH_2), C_{2-4} alkenylene (such as $CH=CH$) or $C(O)NH$;

R^1 represents a C_{1-12} alkyl group optionally substituted by one or more substituents independently selected from cyano, hydroxyl, C_{1-6} alkoxy (such as methoxy or
10 ethoxy), C_{1-6} alkylthio (such as methylthio), C_{3-7} cycloalkyl (such as cyclopropyl), C_{1-6} alkoxycarbonyl (such as methoxycarbonyl) and phenyl (itself optionally substituted by one or more of halogen, nitro, cyano, C_{1-6} alkyl, C_{1-6} haloalkyl (such as CF_3), phenyl(C_{1-6} alkyl) (such as benzyl), C_{1-6} alkoxy, C_{1-6} haloalkoxy, $S(O)_2(C_{1-6}$ alkyl), $C(O)NH_2$, carboxy or C_{1-6} alkoxycarbonyl); or

15 R^1 represents C_{2-6} alkenyl optionally substituted by phenyl (itself optionally substituted by one or more of halogen, nitro, cyano, C_{1-6} alkyl, C_{1-6} haloalkyl, phenyl(C_{1-6} alkyl), C_{1-6} alkoxy, C_{1-6} haloalkoxy, $S(O)_2(C_{1-6}$ alkyl), $C(O)NH_2$, carboxy or C_{1-6} alkoxycarbonyl); or

20 R^1 represents a 3- to 14-membered saturated or unsaturated ring system which optionally comprises up to two ring carbon atoms that form carbonyl groups and which optionally further comprises up to 4 ring heteroatoms independently selected from nitrogen, oxygen and sulphur, wherein the ring system is optionally substituted by one or more substituents independently selected from: halogen, cyano, nitro, oxo, hydroxyl, C_{1-8} alkyl, C_{1-6} hydroxyalkyl, C_{1-6} haloalkyl, C_{1-6} alkoxy(C_{1-6} alkyl), C_{3-7} cycloalkyl(C_{1-6} alkyl), C_{1-6} alkylthio(C_{1-6} alkyl), C_{1-6} alkylcarbonyloxy(C_{1-6} alkyl), C_{1-6} alkyl $S(O)_2(C_{1-6}$ alkyl), aryl(C_{1-6} alkyl),
25 heterocyclyl(C_{1-6} alkyl), aryl $S(O)_2(C_{1-6}$ alkyl), heterocyclyl $S(O)_2(C_{1-6}$ alkyl), aryl(C_{1-6} alkyl) $S(O)_2$, heterocyclyl(C_{1-6} alkyl) $S(O)_2$, C_{2-6} alkenyl, C_{1-6} alkoxy, carboxy-substituted C_{1-6} alkoxy, C_{1-6} haloalkoxy, C_{1-6} hydroxyalkoxy, C_{1-6} alkylcarboxy-substituted C_{1-6} alkoxy, aryloxy, heterocycliloxy, C_{1-6} alkylthio, C_{3-7}

30

5

10

10

15

30

22

30

of halogen, nitro, cyano, C₁₋₆ alkyl, C₁₋₆ haloalkyl, phenyl(C₁₋₆ alkyl), C₁₋₆ alkoxy, C₁₋₆ haloalkoxy, S(O)₂(C₁₋₆ alkyl), C(O)NH₂, carboxy or C₁₋₆ alkoxy carbonyl; R⁷, R⁸, R⁹, R¹⁰, R¹¹, R¹³, R¹⁴, R¹⁶, R¹⁷, R¹⁸, R¹⁹, R²¹, R²², R²³ and R²⁴ are, independently hydrogen, C₁₋₆ alkyl, C₁₋₆ haloalkyl, C₁₋₆ hydroxyalkyl, C₃₋₇ cycloalkyl, C₃₋₇ cycloalkyl(C₁₋₄ alkyl) or phenyl(C₁₋₆ alkyl); and, R¹⁵ and R²⁰ are, independently, C₁₋₆ alkyl, C₁₋₆ hydroxyalkyl, C₃₋₆ cycloalkyl, C₃₋₇ cycloalkyl(C₁₋₄ alkyl) or C₁₋₆ alkyl optionally substituted by phenyl; R²⁵ and R²⁶ are, independently, C₁₋₆ alkyl or phenyl (optionally substituted by one or more of halogen, nitro, cyano, C₁₋₆ alkyl, C₁₋₆ haloalkyl, phenyl(C₁₋₆ alkyl), C₁₋₆ alkoxy, C₁₋₆ haloalkoxy, S(O)₂(C₁₋₆ alkyl), C(O)NH₂, carboxy or C₁₋₆ alkoxy carbonyl); or a pharmaceutically acceptable salt thereof, or solvate thereof, or a solvate of a salt thereof; provided that when T is C(O)NR¹⁰ and R¹ is optionally substituted phenyl then n is not 0; and a histamine antagonist, a steroid, a leukotriene modulator, a human cytokine, a beta-agonist, a phosphodiesterase inhibitor or an antibody.

2. A pharmaceutical combination as claimed in claim 1, wherein Q is a sulphur atom or a group NH, C(O) or NHC(O).
3. A pharmaceutical combination as claimed in claim 1 or 2, wherein T represents a group NH, C(O)NH or NHC(O)NH.
4. A pharmaceutical combination as claimed in claim 1, 2 or 3, wherein X¹, X², X³ and X⁴ are all CH₂.
5. A pharmaceutical combination as claimed in claim 1 wherein the compound of formula (I) is a compound of Example 1 to 416.
6. A pharmaceutical combination as claimed in any one of the preceding claims wherein:

the histamine antagonist is loratidine, desloratidine, fexofenadine, cetirizine, ebastine, astemizole, norastemizole, epinastine or efletirizine;

the steroid is budesonide, fluticasone, mometasone or rofleponide;

the leukotriene modulator is montelukast, pranlukast, zafirlukast, Z4407 or zafirlukast;

the human cytokine is recombinant human IL-10 or IL-12;

the beta-agonist is formoterol, salmeterol or salbutamol;

the phosphodiesterase inhibitor is SB-207499 or theophylline; or,

the antibody is an anti-IL-5 antibody or an anti-TNF-antibody.

10

7. A pharmaceutical composition comprising a compound of formula (I), or a pharmaceutically acceptable salt or solvate thereof, and a histamine antagonist, a steroid, a leukotriene modulator, a human cytokine, a beta-agonist, a phosphodiesterase inhibitor or an antibody, in association with a pharmaceutically acceptable adjuvant, diluent or carrier.

15

8. A pharmaceutical combination as claimed in any one of claims 1 to 6 for use in therapy.

20

9. A pharmaceutical combination as claimed in any one of claims 1 to 6 in the manufacture of a medicament for the treatment of asthma or rhinitis.



INVESTOR IN PEOPLE

Application No: GB 0104534.3
Claims searched: 1-9

Examiner: Dr Annabel Ovens
Date of search: 9 July 2002

Patents Act 1977 Search Report under Section 17

Databases searched:

UK Patent Office collections, including GB, EP, WO & US patent specifications, in:

UK Cl (Ed.T): A5B

Int Cl (Ed.7): A61K 31/4468, 31/4523, 31/4525, 31/453, 31/4535, 31/454, 31/4545, 31/46, 31/496, 31/497, 31/498, 31/506, 31/517, 31/519, 31/52

Other: Online: PAJ, EPODOC, WPI, CAS-ONLINE

Documents considered to be relevant:

Category	Identity of document and relevant passage	Relevant to claims
X, E	WO 02/32893 A2 (SCHERING) see page 10 lines 16-18, page 11 lines 3-20 and page 19 lines 6-16	1 at least
X, E	WO 01/60407 A2 (ASTA MEDICA) see page 7 lines 22-34	1 at least
X	WO 98/06394 A1 (SCHERING) see page 3 line 30-page 4 line 6, page 4 lines 17-29 and Examples 8-11	1 at least
X	US 6103735 (ASLANIAN AND PIWINSKI) see column 2 lines 45-54 and column 5 line 59-column 6 line 7	1 at least
X	CAPLUS Abstract Accession No. 2001:79915 & BioDrugs Vol. 14, No. 6, 2000, D Reichmuth and R Locky, "Present and potential therapy for allergic rhinitis. A review", pages 371-387 (see abstract)	1 at least

X	Document indicating lack of novelty or inventive step	A	Document indicating technological background and/or state of the art.
Y	Document indicating lack of inventive step if combined with one or more other documents of same category.	P	Document published on or after the declared priority date but before the filing date of this invention.
&	Member of the same patent family	E	Patent document published on or after, but with priority date earlier than, the filing date of this application.